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THE CLINICAL APPLICATIONS OF SPECIFIC THERAPY

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BIOLOGICAL ANTAGONISTS to be clinically valuable must have a profound effect upon invading parasites, or disordered bodily structures with a minimum effect on normal tissues. Ideally, they should combine with enzyme systems within the bacterial organisms, overactive cells of the body, or neoplastic cells that are unique to these structures, and are not possessed, at least to the same extent, by the normal cells of the patient being treated. Biological antagonists are most useful, therefore, when they are relatively non-toxic to the human organism in concentrations effective against the living structures which are the targets of therapy. These criteria are possessed to a high degree by most of the antibacterial agents in current use and true cures can be obtained by their application. Unfortunately, many of the biological antagonists which are effective against neoplasms, leukæmia, and overactive endocrine glands are relatively toxic in the concentrations used and they have adverse side effects limiting their usefulness. They must be administered under careful supervision, and they effect temporary remissions rather than cures.

Because of the very widespread application of antibacterial chemotherapeutic agents and antibiotics in combatting the parasitic invaders encountered every day in the practice of the healing art, these will be discussed first. The remainder of the article will be devoted to other clinically useful agents which, by substrate competition, interfere with various normal or pathological bodily functions.

ANTIBACTERIAL CHEMOTHERAPY

1. Sulphonamides
2. Antibiotics
   - (*a*) Penicillin
   - (*b*) Streptomycin
   - (*c*) Aureomycin
   - (*d*) Chloromycetin
   - (*e*) Others

THE SULPHONAMIDES. These valuable substances, of known composition, have been used for thirteen years, and during that time have been responsible for saving a very great many lives. They act by preventing the incorporation of para-amino benzoic acid into folic acid within the bacterial organisms. This metabolic mechanism is essential to gram positive organisms when they are growing, only. The sulphonamides, by acting as an antagonist to para-amino

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benzoic acid, exert a bacteriostatic effect upon the invading organisms, in the concentrations of these drugs that are usually obtained in the body. The effect, however, is not apparent until after several cell divisions, so that clinical improvement takes 24 to 72 hours to occur. The sulphonamides do not effect non-growing organisms or bacteria that can grow without synthesizing folic acid such as *B. coli*, *E. typhosa*, *H. influenzae*, the tubercle bacillus, etc. Further, the presence of para-amino benzoic acid in pus or tissue exudates antagonizes the sulphonamide being used. One cannot expect therapy with the sulphonamide drugs, therefore, to eradicate even sensitive organisms in the middle of a pocket of pus in a Brodie's abscess or appendiceal abscess. Non-growing organisms quietly resting in a devitalized sequestrum will not be touched, and they will linger there until some future date, ready to cause trouble long after the chemotherapy has been discontinued, unless surgical procedures are taken to remove the dead tissue.

Of all the sulphonamides, sulphadiazine contains the optimal anti-bacterial potency. It can only be improved upon in regard to its toxicity. The usual initial dose is 6 Gm. (2 Gm. every two hours for three doses) followed by 3 to 6 Gm. daily in divided doses every four hours by mouth. The drug is fairly rapidly absorbed and excreted, and the above regimen is aimed at quickly building up an effective blood level and maintaining this value throughout the course of therapy. A satisfactory plasma concentration is 7.0 to 10.0 mg. per 100 cc. of blood, that is, this level will be bacteriostatic to invading organisms. Sulphadiazine is most useful against hæmolytic streptococci, the gonococcus, meningococcus and most pneumococci. It penetrates the meninges fairly well and is still the most useful drug in combatting cerebro-spinal fever.

Many variations of the sulphonamides have been made by changing the side chains in the molecular structure, such that the toxicity is lessened, or absorption and excretion rates are altered. Thus, sulphamerazine is more slowly absorbed and excreted than sulphadiazine, and sulphaguanidine and sulphthiadiazole give a high concentration in the gut by virtue of their very slight penetration of the gastro-intestinal mucosa. Sulphasuxidine and sulphathalidine were designed for a slow release of the active drug and a more prolonged action. The effective dosage of each of these varies somewhat from that given above for sulphadiazine, because of their varying absorption rates and because changes in molecular structure alter their anti-bacterial potency, and toxicity.

Toxicity is due either to excessive dosage or sensitivity. Repeated courses of any one sulphonamide increase the likelihood of the latter. Fever, dermatitis and interference with the production of leucocytes are the commonest complications. Renal damage usually occurs in dose-related fashion and may vary from crystalluria with a little hæmaturia to severe lower nephron nephrosis with oliguria or anuria, uræmia and the possibility of a fatal outcome. Alkalinization of the urine reduces the incidence of both crystalluria and toxic nephrosis. To avoid these complications, daily fluid balance measurements, and repeated urinalyses and leucocyte counts should be carried out during the time that the patient is on sulphonamide therapy.

Penicillin. Penicillin is one of the most useful and innocuous antibiotics known. It is not one substance, but

four. There are penicillins X, G, F, K, in order of their potency within the body. The *in vitro* potency is in the reverse order, but the *in vivo* potency depends on the extent that they bind to plasma protein. Their action is somewhat similar to the sulphonamides since they interfere with the oxidation-reduction mechanisms necessary for the growth of bacteria. Penicillin is most useful in streptococcal infections, pneumococcal pneumonia, subacute bacterial endocarditis, gas gangrene, gonorrhœa, syphilis and actinomycosis. There are several disadvantages to penicillin, however. It must be given intramuscularly, since it is poorly absorbed from the stomach and intestines, and it is inactivated by penicillinase produced by *B. coli* organisms growing within the gut. Further, it is very rapidly absorbed from its depot in muscle and even more rapidly excreted by the kidneys. Various successful efforts to prolong its action have been made, however. The administration of a substance called Caronamide greatly slows the tubular excretion of penicillin and enables a satisfactory blood level to be maintained for several hours longer, but more useful still are the various additions to penicillin which slow its absorption from muscle. The best preparation to date is procaine penicillin G aluminium monostearate. It has a prolonged action, and when 300,000 units are given intramuscularly at one time a satisfactory blood level can be maintained for at least 48 hours.

Penicillin exerts its bacteriostatic effect at a definite threshold level for each bacterial species, so that a dose of 20,000 units every 3 hours with a blood penicillin level of 0.25 units usually proves adequate to suppress the growth of the pneumococcus in 24 to 48 hours, whereas 60,000 units every 3 hours and a plasma level of 0.5 to 2.0 units per cc. for four weeks or longer is required to successfully treat subacute bacterial endocarditis due to *Streptococcus viridans*. This also reveals that to treat more resistant organisms successfully, both dosage and duration of therapy are important. In syphilis, on the other hand, the time interval is more important than either the total amount of penicillin given or the plasma concentration of penicillin. Early syphilis can be adequately treated by 600,000 units of procaine penicillin G aluminium monostereate, intramuscularly, every second day for a period of two weeks, but massive single dose therapy giving 5,000,000 units (about the same total dose) fails to achieve satisfactory cures.

STREPTOMYCIN. This antibiotic proves useful in the treatment of chronic urinary infections, Friendlander's pneumonia, *Shigella* dysentery, *H. influenzæ* meningitis, *Salmonella* meningitis, and various types of tuberculosis. Streptomycin has its limitations, however, and it is ineffective in *Salmonella* enteritis, caseating tuberculosis, or pulmonary tuberculosis with cavitation. Although *Brucella abortus* and *E. typhosa* are sensitive to streptomycin *in vitro*, typhoid fever fails to respond to streptomycin, and undulent fever needs the synergistic action of sulphadiazine and streptomycin before clinical remissions are obtained. Penicillin is not synergistic with streptomycin, therefore there is no advantage in giving the two together, unless superinfection with penicillin-sensitive organisms occurs.

Streptomycin is poorly absorbed from the gastrointestinal tract and it must be administered intramuscularly. The usual does is 1 to 3 Gm. daily in two divided doses at twelve hour intervals. This results in blood levels of 10 to

40 microgm. per cc. A 14-day course of therapy is adequate for many of the illnesses caused by streptomycin sensitive organisms, but in tuberculosis the above dosage schedule must be maintained for 60 days or longer.

Unfortunately, toxicity due to streptomycin is common. It occurs in dose-related fashion, and the duration of therapy is the critical factor. Few patients can stand treatment for 60 to 120 days without damage to the cochlear and vestibular divisions of the eighth nerve, resulting in tinnitus, deafness and ataxia. These complications definitely limit the usefulness of streptomycin in the treatment of tuberculosis. Urticaria, fever and chills due to the drug are not uncommon. Streptomycin in high concentration, that is over 100 microgm. per cc. of blood may cause an unusual and serious type of fatty degeneration in the liver and kidneys.

Dihydrostreptomycin is a little less toxic than streptomycin, but it has a tendency to cause anorexia, whereas streptomycin often stimulates appetite and well-being.

Chloromycetin (Chloramphenicol). This drug may be given orally, since it is readily absorbed from the gut. It is effective against rickettsia, viruses of the psittacosis, lymphogranulome venereum group, *E. typhosa*, *Salmonella*, *B. abortus* and *H. pertussis*. It is not effective against the tubercle bacillus. In other respects its antibiotic spectrum is similar to streptomycin. The recommended dosage is 0.5 Gm. every four hours for one day, then every six hours daily until a total of 17 to 25 Gm. has been given. A plasma level of 0.5 to 8.0 microgm. per cc. is obtained this way.

In typhoid fever it causes a rather slow defervescence of the fever and symptoms and leaves much to be desired. Relapses with bacteræmia may occur, and serious complications such as perforation must still be watched for. It may not cure the typhoid carrier state. It proves effective, however, in urinary tract infections due to *B. coli* which may stubbornly resist other forms of therapy. By virtue of its low toxicity, chloromycetin has become popular in some centres for the treatment of pneumonia in children. The oral route of administration is also a great advantage in treating children.

Aureomycin. Aureomycin can also be given orally. It is the second antibiotic to prove useful against rickettsia and viruses. Infectious mononucleosis, primary atypical pneumonia, and herpes zoster may yield to this drug. *Brucella* organisms, *H. influenzæ*, and many gram positive cocci are inhibited by it. *Staphylococcus aureus hæmolyticus* which is inherently penicillin resistant gives way to aureomycin. The usual dosage is 20 to 30 mg. per kilogram of body weight per day in divided doses every three to four hours. This provides an effective blood level of 1.0 to 4.0 microgm. per cc.

Aureomycin not infrequently causes nausea, vomiting and diarrhœa and these symptoms may force one to discontinue the drug. If continued in large doses for periods longer than a week or so, it may cause considerable metabolic disturbances in the body.

Other Antibiotics. There are many other antibiotics such as polymyxin, bacitracin, subtilin, subtenolin, baccilomycin and tyrothricin which are clinically useful but have narrower spectra of antibacterial activity than the four substances discussed in more detail above. They are useful in certain selected cases, but some of them possess considerable toxicity, and others can

only be used as surface applicants. A full discussion of them is beyond the scope of this article.

Resistance to the Antibacterial Substances. Resistance depends upon the development of mutants by the target organisms, so it is not the patients but the bacteria that become refractory to the antibacterial drugs. There are always some naturally occurring mutants but most arise *de novo* after contact of the bacteria with the drug. The mutants develop an alternative metabolic pathway to the enzyme system blocked by the drug, and in so doing gram positive organisms become more gram negative. Resistance proceeds stepwise with each mutation for most organisms that acquire sulphonamide or penicillin resistance, but strangely enough the tubercle bacillus may acquire a full blown streptomycin resistance with the first mutation after exposure to this drug.

The mass prophylaxis programs carried out by the United States Armed Forces in 1943 produced very resistant strains of hæmolytic streptococci which prior to this time were sulphonamide sensitive. These resistant strains have persisted since. In the case of sulphonamide therapy, inadequate dosage allows the organisms to acquire resistance, therefore the aim of therapy should be to build up a high initial concentration of the antibacterial substance in the cells and fluids of the body to get rid of the organisms as fast as possible. The dosage and plasma level obtained, of course, depend on the toxicity of the antibacterial substance to the host. An innocuous antibiotic like penicillin can be given in such huge doses, if need be, that the Na, K, or Ca ions attached to it will cause more trouble than the penicillin itself, but the recommended doses of sulphonamides, on the other hand, are very close to the upper limits of tolerance for the human organism. The resistance of the tubercle bacillus to streptomycin is a little different. It does not depend on the size of the daily dose or the frequency of doses during the day, because the incidence of resistance increases with the duration of therapy. The organism may be sensitive to 1 microgm. of streptomycin per cc. the day before therapy is started and resistant to 1000 microgm. per cc. after 30 to 50 days of treatment. The possibility of resistant organisms should be considered whenever the antibacterial biological antagonists fail to achieve the expected therapeutic result.

BIOLOGICAL ANTAGONISTS IN NEOPLASTIC DISEASE

1. Urethane
2. Nitrogen Mustard Compounds
3. Folic Acid Analogues
4. Gonadal Hormones

Urethane. Ethyl carbamate (urethane) is a growth suppressant that has assumed a useful role in the treatment of chronic myeloid leukæmia and multiple myeloma. It causes a transient increase in mitoses in normal or neoplastic tissue, then a retardation of growth. With therapeutic doses, a fall in leucocyte count occurs with regularity due to its effect on the bone marrow. Administration of larger amounts of urethane causes a severe depression of the bone marrow with leukopenia, thrombocytopenia and anæmia. It is also a hypnotic in large doses. Urethane is occasionally successful in temporarily suppressing the growth of inoperable disseminated cancer, but generally there is no improvement.

Urethane is prepared as an elixir or as enteric coated capsules and is given

orally. In amounts of 2 to 6 Gm. daily, for periods of two to eight weeks, it may cause effective remissions in chronic myeloid leukæmia. The leucocyte count begins to fall toward normal in one to three weeks, and there is a rise in hæmoglobin and red cell count. Its effect is comparable to radiation therapy, and just as with X-ray, repeated courses may be given. Multiple myeloma requires more intensive therapy. Three to 6 Gm. per day of urethane for a period of thirty days followed by 1 to 1.5 Gm. per day for another 60 to 90 days may be required before an appreciable reduction of the myeloma cells in the marrow, relief of bone pain, and a decrease in the abnormally high globulins in the blood occurs. Unfortunately, in both chronic myeloid leukæmia and multiple myeloma relapses may occur within two to three months of the cessation of therapy, and indeed, relapse sometimes occurs while the treatment is still being given. The best that can be hoped for in the way of remission is a period of 8 to 10 months without further therapy.

Urethane generally causes no improvement in chronic lymphatic leukæmia, acute leukæmia, Hodgkin's disease, or lymphosarcoma.

Nitrogen Mustard. Nitrogen mustard (methyl, bis(betachloroethyl) amine hydrochloride) is a very toxic compound derived from mustard gas. It exerts its effect by extremely rapid decomposition within the body resulting in ionization of cells. The effect is closely similar to radiation therapy. Some of the chromosomes are knocked out and this interferes with cell respiration or growth. Its action is more widespread throughout the body than radiation but there is more rapid recovery from the toxic effects than with an equivalent amount of radiation. It effects those cells with the highest metabolic activity such as the bone marrow elements and the columnar epithelium of the gastro-intestinal tract.

N-mustard is administered intravenously in a dose of 0.1 mg. per kilogram of body weight daily for four days. This causes a leukopenia and thrombocytopenia in 7 to 14 days with recovery in about 21 days. Occasionally the above dosage exceeds the safe level, especially if the bone marrow is already depressed, and severe leukopenia, thrombocytopenia, purpura, fever and weakness are caused. There may be a very rapid onset of anæmia. Recovery starts in 4 to 10 days but during the interval of severe depression of the marrow transfusions and penicillin are required.

N-mustard is useful in disseminated and pulmonary Hodgkin's disease, widespread lymphosarcoma, reticulum cell sarcoma and mycosis fungoides, but it is not a cure. Remissions last from 2 to 52 weeks but only average 6 weeks. Radiation therapy is better for localized Hodgkin's disease of lymphosarcoma. N-mustard is sometimes helpful in inoperable carcinoma of the lung. It has been reported to give some relief in 50 to 70 per cent of cases for periods of 2 weeks to 2 months. It has been tried with success in polycythæmia vera.

A variant of N-mustard is beta, naphthylamine, di-chloroethylamine, called R-48 for short. This drug can be given orally in doses of 100 to 300 mg. daily. It has a slower and more prolonged action than N-mustard, and it has caused partial remissions for some months in chronic lymphatic leukæmia and lymphoblastoma.

Substances of quite different nature but with somewhat similar metabolic effects

are radioactive iodine, I^{131}, and radioactive phosphorus P^{32}. The former is effective in 15 per cent of carcinomata of the thyroid, and the latter is useful in polycythæmia vera and lymphoblastoma.

Folic Acid Antagonists. Many analogues of the nutritionally active substance, pteroyl glutamic acid (folic acid) have been prepared since 1946, but the two compounds which have received the most extensive clinical trials are aminopterin (4, aminopteroylglutamic acid) and A-methopterin (4, aminomethylpteroylglutamic acid). They act as biological antagonists to folic acid and only minute amounts are required to effectively interfere with the vitamin, but they also act on biochemical systems more important and subtle than simple competetive substitution of aminopterin or A-methopterin for folic acid. These substances are the first biological antagonists to effectively cause remissions in acute leukæmia.

Aminopterin may be given intramuscularly or orally in amounts of 0.5 to 1.0 mg. per day. Sometimes higher initial doses are given. A-methopterin is less effective and 2.5 to 5.0 mg. per day are required. Usually 10 to 30 mg. of aminopterin are all that can be tolerated in one course of treatment because of the toxic effects of the drug. Stomatitis, ulcerated mucous membranes, sore smooth tongue, diarrhœa, and agranulocytosis may occur. Treatment must be stopped at the first sign of stomatitis. These complications cannot be overcome by giving large amounts of liver extract or even 200 mg. per day of folic acid itself. Despite these objections therapy with the folic acid antagonists can achieve satisfactory remissions in 15 to 20 per cent of children with acute leukæmia and a smaller proportion of adults. A remission consists of a reduction in the size of the liver and spleen, a rise in hæmoglobin and erythrocyte values to normal, a fall in leucocyte count, and subjective improvement. Remissions of 8 months in adults, and over 2 years in children have been reported. In the treatment of acute leukæmia these substances leave a great deal to be desired, but at the same time they open up a whole new avenue of approach in both the investigation and treatment of leukæmia.

Gonadal Hormones. Androgens and Oestrogens exert their beneficial effect in neoplastic disease by opposing each other, thus oestrogens are beneficial in carcinoma of the prostate, and adrogens sometimes suppress metastases from carcinoma of the breast.

One to 5 mg. per day of stilboestrol is effective in 50 to 75 per cent of cases of carcinoma of the prostate. It requires 7 to 10 days for any beneficial effect to appear, then there is a reduction in prostatic size, relief of urethral obstruction, a degeneration of neoplastic cells in the primary and metastases, a decrease in bone pain, and a fall in serum alkaline phosphatase. An inoperable tumour may be converted to an operable one. It causes loss of libido and some growth of the breasts, but this can be tolerated.

Testosterone is not so useful as the oestrogen compounds but occasionally in doses of 100 mg. intramuscularly three times a week it will cause a partial remission and relief of pain in bone metastases from carcinoma of the breast. It is stated that it helps 20 to 30 per cent. Improvement is seen in 10 to 14 days if it is going to occur. Unfortunately, soft tissue metastases may continue to progress while treatment is being given. Testosterone causes a certain amount of increased libido and musculinization.

OTHER USEFUL BIOLOGICAL ANTAGONISTS

1. Thiouracil
2. Dicumarol

THIOURACIL COMPOUNDS. Thiouracil, and its less toxic relatives, propylthiouracil and methylthiouracil stop the production of thyroxin, and cause a fall in protein-bound iodine in the blood and the iodine content of the thyroid gland. The exact site of action of thiouracil is not known, but it may act by preventing the release of I_2 from iodide or by inhibiting the enzymatic peroxidase system that functions to oxidize I_2 in the formation of the thyroxin molecule. These compounds do not prevent the thyroid gland from absorbing iodine.

The usual daily dose is 600 mg. of thiouracil, 150 - 300 mg. of propylthiouracil, 500 mg. of methylthiouracil. These dosages are usually sufficient to reduce the elevated B.M.R. to normal and diminish the symptoms, except for exophthalmos. The thiouracil compounds are used mainly for preoperative therapy and they have reduced the mortality of thyroidectomy from 1.5 to 2.0 per cent down to approximately 0.1 per cent. In adolescent goitre, in thyrotoxicosis complicated by severe cardiac disease or in patients refusing operation, one can maintain remissions for long periods with propylthiouracil or methylthiouracil, provided there is adequate control of therapy. Relapses usually occur soon after the withdrawal of the drug, but in some patients prolonged remissions are obtained.

Toxicity consists of agranulocytosis, and is a complication in 9 per cent of those on thiouracil, but only 1-2 per cent of those treated with propylthiouracil.

DICUMAROL. This substance, by suppressing the production of new prothrombin in the liver through competition with vitamin K, interferes with the ability of the blood to clot. By so doing, it has proved itself to be a most useful drug in the treatment of coronary thrombosis, and phlebothrombosis, and it reduces the mortality from pulmonary infarction from 25 per cent to 12 per cent. 300 mg. of dicumarol are given orally the first day of therapy, followed by 200 mg. the second day; the dose after that is adjusted to the prothrombin time which should be kept between 15 and 30 per cent of normal for the one-stage method. Treatment needs to be continued for 21 to 28 days to prevent effectively further thrombosis.

Complications are due to hæmorrhage. About 8 to 10 per cent have hæmorrhagic complications. Giving "bank blood" may dilute the patient's circulating prothrombin and induce bleeding in patients on dicumarol.

CONCLUSION

This brief review of clinically useful biological antagonists is aimed at arousing your interest in a new field of investigation and treatment which not only enlarges the therapeutic spectrum of both physician and surgeon, but promises much in the investigation of the ætiology of disease.

FOREFEET AND FAULTY FOOTWEAR

F. P. DEWAR, M.D.

The attendance at the Foot Clinic of the Toronto General Hospital is overwhelmingly female. This imbalance is again noted in the offices of chiropodists, and of doctors who are interested in foot problems of adults. It is not apparent when dealing with children but becomes so in early adult life and increasingly so as the years pass. In addition, it is observed that the increased ratio of female to male is largely due to complaints related to the forefoot. These complaints stem from well recognized abnormalities that have occurred in feet once apparently normal. Cavus feet with clawing of the toes, though notoriously associated with forefoot pain, are seldom encountered. Rheumatoid arthritis, with its strong predilection for women, is only a minor factor. Congenital deviations from the mean have no sex linkage nor have other common predisposing causes of foot pain such as increased weight or positions requiring long hours of standing. The only stress to which the feet of women are subject and from which the remainder of the population escape is provided by the peculiar type of foot wear to which they are so partial. Whether this stress is sufficient, in certain cases, to be the basic cause of the abnormality or only acts to produce symptoms once the abnormality has developed is still open to argument. We must be content, at present, to recognize the fact that once given suitable clothing the majority of these painful feet are relieved though the deformity is not one whit altered. There are, of course, multiple causes of forefoot pain, but this article deals only with those that appear to be most clearly linked with the modern fashionable shoe.

HIGH HEELS AND NARROW POINTED SHOES

The great bulk of women's shoes are at fault. The heel is too high and the forepart of the shoe malshaped. The heel acts as a labour saving device for the calf muscles, sparing them an equivalent height of anti-gravity action. Women's heels are exaggerated at fashion's decree to make their ankles appear slimmer. As a result the heads of the metatarsal bones meet the horizontal almost perpendicularly resembling those in a severe cavus foot. The toes are dorsiflexed. Their owners have chosen to tiptoe their way through life throwing an abnormal strain on the ball of the foot while the weight-bearing properties of the heel are to a large extent dispensed with. This same device is used therapeutically to assist patients suffering from plantar fasciitis or those with injuries of the tendo Achilles. The front of the popular shoe is slender and tapers to a point on the centre line. This balanced wedge bears little resemblance to the unbalanced wedge of the normal foot, whose longest length is medial sloping gradually to the little toe. When such a shoe is worn it crowds the flanking toes toward the third in an unmerciful manner. Driven by the entire weight of the body the foot slides downwards from the pinnacle of the heel only to be caught cruelly in a wedge-shaped vise.

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The requirements of the transverse metatarsal arch are seldom met in these slender shoes. To please the purchaser they are fitted to the relatively narrow non-weight bearing foot. If on standing a complaint of tightness is made a wider fitting is tried, but owing to the peculiar sizes it is frequently found that the roomier shoe does not grip the heel properly and difficulty is encountered trying to keep it on. The narrower one is accepted. The discomfort of "breaking in" a pair of shoes is due to the efforts of the foot to overcome this lateral compression by stretching the uppers, and evidence of this is available to the most casual observer on the streetcar or in the cupboards of his women folk. Forefoot crumpling enhances the difficulty of an even distribution of weight across the ball of the foot, and tends to produce localized pressure areas on the sole, while the ends of the arch in contact with the uppers of the shoe are particularly liable to pressure lesions in the form of bunions.

HALLUX VALGUS AND HAMMER TOES

Feet with wide transverse arches and those with long toes are more prone to discomfort in the average shoe because of the difficulty of obtaining even a reasonable fit. Broad forefeet are commonly associated with metatarsus primus varus which is a lack of parallelism between the first and second metatarsal bones. The first is medially angulated at its base and the head of the first and second more widely separated than normally found. The great toe is maintained in line with the shaft of this deviated metatarsal by muscle balance and lacks the close support of the second toe. When such a foot is encased in a narrow pointed shoe the great toe must of necessity be levered laterally at the metatarso-phalangeal joint and crowded toward its fellows. This is but one of the factors in the development of Hallux Valgus yet is is an important one, for, once the normal linear arrangement of digit to its metatarsal is lost, muscle imbalance, adaptive capsular change, and indeed the normal take-off while walking all tend to increase the deformity. Pressure of the shoe over the now prominent metatarsal head creates a bunion with its underlying exostosis. The first toe drifts farther laterally against the second toe and often comes to lie underneath it, forcing it into a cock-up or hammer toe position.

Unless the shoes are full and rounded in front and laterally to allow proper extension, the digits may be severely crowded. This is especially true of people with long toes. Mallet toes, those with a flexion deformity of the distal joints, are not disabling unless corns develop on their tips from pressure on the sole of the shoe when walking. Hammer or cock-up toes are more worthy of notice. In this type the flexion deformity occurs at the proximal interphalangeal joint, the distal joint being sometimes neutral but more often hyperextended. The metatarsophalangeal joint is always extended (dorsiflexed), the base of the phalanx pressing downwards on the head of the metatarsal. Due to this abnormal vertical position of the proximal phalanx it acts as a strut transmitting pressure from the upper of the shoe and forcing the head of the metatarsal into the sole of the foot, a frequent cause of ball callouses and metatarsalgia. The pull of the long tendons also tends to shorten the toes by increasing the degree of folding and this adds to the deformity. In some instances the deformity may

progress sufficiently to dislocate the metatarso-phalangeal joint. Pressure points on the dorsal surfaces of the prominent knuckles develop painful corns. Clawing of the toes is in all probability due to imbalance between the long and intrinsic muscles of the foot and can certainly develop without any evidence of crowding of the toes in tight shoes as in progressive muscular atrophy. Nevertheless, no satisfactory explanation has been brought forward for its occurrence in adults who have once had normal feet and who show no evidence of any neuromuscular disorder. It is justifiable to assume, therefore, that there is a close alliance between hammer toes and the type of shoe that, by its very shape, would squeeze the toes into such a position.

Between crowded toes minor troubles may arise. Perspiration gathers in the web and causes cracking which produces distressing though easily relieved symptoms. Also at localized pressure points soft corns develop which are the counterpart of corns elsewhere but are modified by their moist environment, and are often more painful. It is necessary that the toes should spread slightly inside the shoe so that the air currents engendered by walking will evaporate perspiration which would otherwise accumulate.

PAIN IN THE FOREFOOT

The patient comes complaining of pain in the forefoot and the cause of this must be sought in an orderly fashion. It often stems from localized pressure and its sequel a corn or bunion. One must bear in mind the frequent occurrence of plantar warts at these points. They may be distinguished by shaving the surface with a sharp knife; their punctate appearance differs from the crystal clarity of a simple hyperkeratosis. Metatarsalgia, a deep-seated pain related to one or more of the lateral four metatarso-phalangeal joints is less readily understood. Unequal weight transmission is the commonest cause and is associated with a prominence of the head of the bone in the sole and a callosity of the overlying skin. Trauma and bruising of the tissue occurs between the head of the metatarsal and the sole of the shoe. The pain appears with weight bearing and persists until relief is obtained by sitting down. If it is not very acute symptoms may not develop until late in the day, or until a certain amount of walking has been accomplished. The area is tender and may be swollen; when acute it is very disabling. Morton's metatarsalgia is somewhat different. Tight shoes may play no part in its etiology but as widespread recognition of this syndrome is lacking it will bear a short description. This pain occurs in attacks precipitated by walking or standing and is almost always located between the heads of the third and fourth metatarsals in the ball of the foot and radiates into either or both of the corresponding toes. Between attacks which are severe enough to encourage the sufferer to remove the shoe the foot is painless and to all intents normal. The cause of this pain is irritation by a pressure probably from the adjacent metatarsal heads of a neuroma near the site of division of the digital nerve. The development of the neuroma is not understood. Many cases of metatarsalgia cannot be explained on these bases and one must watch for arthritic involvement of the metatarso-phalangeal joints, ischemia of the intrinsic muscles of the foot, March fracture and Freiberg's disease of the metatarsal heads. These rarer causes of painful forefeet, while not

so clearly related to ill-fitting shoes, are sometimes aggravated by them and much relief can be obtained by correction of this.

RELIEF OF PAIN

Operations are seldom necessary to obtain relief from symptoms in these types of feet. It is more important to understand the correct fitting of shoes and the proper use of metatarsal bars and pads. The shoe must be roomy enough to house the weight-bearing foot and must therefore resemble its outline. It should have a straight inner border extending from the heel to the head of the first metatarsal and along the medial border of the great toe; a rounded antero-lateral border allowing full extension of all the toes as occurs when walking barefoot; a moderate heel not more than two inches high. It should be preferably an Oxford type shoe constructed of leather with rubber heels if desired. The back of the shoe should fit the heel snugly. The widest part of the sole must accommodate all the metatarsal heads or the full width of the ball of the foot when weight bearing. The posterior border of an obliquely transverse band (corresponding to the ball of the foot) is marked on the sole of an old shoe by the junction of the shank and the worn part of the sole. The band extends forward about an inch and its anterior border is delineated by the breaking line of the shoe. The correct placement of the ball of the foot over this imaginary band is one of the secrets of proper fitting. If the head of the first metatarsal is correctly placed there is little need to worry about the overall length; and if the width is correct there is no necessity to fret about room for the toes. The shoe is held in proper position by the uppers and laces that cross the dorsum of the foot. The uppers should not meet in the midline but leave a gap allowing the laces to take up the slack. This will prevent pumping of the foot in the shoe. In some low arched feet this fitting is impossible and a pad must be added behind the tongue to obtain the correct adjustment.

When hammer toes are present there is need for extra room which can only be obtained by constructing the front uppers of soft yielding leather. To obtain this ample accommodation an oversized shoe may be necessary or the correct size stretched. There must be no remaining pressure points between the dorsum of the toes and the uppers of the shoe or pain will not be relieved.

A metatarsal pad is supposed to extend the weight-bearing area of the ball of the foot and not to act as a jack for elevation of a depressed metatarsal head. It is placed directly behind the callous or pressure point and is high enough to fill in the space between the shaft of the bone and the sole of the shoe. It must be held firmly in place by a thumbtack as well as rubber cement or else it will be wiped backwards to a disadvantageous position by walking. Any depression of the head of a metatarsal is better dealt with by a hollow made in the sole of the shoe or by an insole similarly adjusted. Placement of pads in new shoes is best delayed until the feet have watermarked them as their own. Pads are of greatest value in cases of metatarsalgia that are not severe and that are not complicated by bad hammer toes.

A metatarsal bar is reserved for the more severe cases of forefoot pain. It is made of a band of leather about one-quarter of an inch in height and one-and-a-half inches wide and is placed

obliquely across the sole of the shoe just behind the weight-bearing portion of the sole. If placed further forward it will lie under the metatarsal heads and will defeat its own purpose. It acts by tilting the foot into a dorsiflexed position and throwing more weight on the heel and also as a strut to transmit weight through the shafts of the metatarsals, under which it lies, to the ground. Both these factors short circuit the ball of the foot as a weight-bearing unit and relieve pressure pain. As the bar wears down, its effectiveness is reduced and the symptoms are apt to recur. Also, bars of this type are of little value if walking must be done on soft ground for they lose their purchase.

HOPE

At the present time there is no link between the fashionable and the sensible shoe. Much can be done to improve the appearance of the so called "corrective" shoe but there are limits to this possibility imposed by the rigid qualifications necessary in such a last. Children's feet are not subject to fashion and their excellent shoes are examples of much thought and planning. Men's footwear is of similar design and forefoot troubles are rarely a cause of complaint. Education is needed to encourage women to discard this adolescent folly that underlies so much discomfort. There is no difference in the shape of the male and female foot. Both require adequate footwear if they are to perform their function well. It is time to realize that it is fashionable to be comfortable.

THE CANADA YEAR BOOK, 1948-49

Containing 1300 pages of statistics, maps, diagrams and other data, this official publication of the Dominion Bureau of Statistics is an invaluable, interesting reference book. Special features include a statistical summary: 1871-1948, a directory of sources of official information, an outline of Dominion legislation, numerous maps and diagrams and many other features. *Bona fide* teachers and university students can purchase paper-bound copies for $1.00 by applying to the Dominion Statistician, Dominion Bureau of Statistics, Ottawa.

INTERVERTEBRAL DISC LESIONS AND SCIATICA

J. A. RUTHERDALE, 5T0

TWENTY YEARS AGO the relationship between ruptured intervertebral discs and sciatica was unknown. Today this relationship provides the basis of a clinical entity curable, in many cases, by operative means. In the past, sciatica was believed to be due to a primary affection of the nerve root or nerve sheath. Now it is believed that, while a few cases of sciatica may be due to a primary neuritis or radiculitis, the majority of cases are attributable to protrusion of an intervertebral disc with pressure on spinal nerve roots. This new viewpoint concerning the aetiology of sciatica is based on the painstaking work of Schmorl who examined a large number of spines at autopsy and first elucidated the pathology of the intervertebral disc.

ANATOMICAL CONSIDERATIONS

Each intervertebral disc is composed of an outer ring of fibrous and elastic tissue termed the annulus fibrosus and a central portion of soft pulpy material known as the nucleus pulposus. Thin cartilaginous plates separate the disc from adjacent vertebrae.

The intervertebral disc forms the anterior wall of the spinal canal at the level of nerve roots passing laterally to emerge from the spinal canal through the intervertebral foramina. The relation of the fifth lumbar nerve to the disc between the bodies of the fourth and fifth lumbar vertebrae and the relation of the first sacral nerve to the lumbosacral disc are especially important since 98 per cent of lumbar disc lesions occur at these levels.

A knowledge of the distribution of these two nerve roots aids in the localizing of disc lesions. Briefly, the fifth lumbar dermatome includes the area of skin on the front of the shin and on the inner part of the foot, and the motor fibres of the fifth lumbar root are distributed chiefly to the anterior tibial group of muscles. The first sacral nerve root supplies sensory fibres to the outer side of the leg and foot and motor fibres to the calf muscles.

AETIOLOGY AND PATHOLOGY

Repeated trauma, resulting in weakening of the annulus, is believed to be the prime aetiological factor in disc prolapse. As this is a rare lesion in animals it may be that man's assumption of the upright posture with increased strain on the intervertebral disc accounts for the degenerative changes seen commonly in the annulus. Symptoms occur when some additional strain is imposed on the disc causing the nucleus to extrude through the weakened annulus and press on spinal nerve roots.

About half of the protrusions occur between the fifth lumbar and first sacral vertebrae. Almost an equal number occur between the fourth and fifth lumbar vertebrae.

The sex incidence is predominantly male (3: 1) and this is probably due to a greater exposure to trauma.

Although the degenerative changes probably begin in adolescent or early adult life, symptoms usually do not occur until later when some additional strain causes the disc to herniate.

The exact site and size of the protrusion vary and these factors bear an important relationship to the symptomatology. Small mid-line protrusions are seen commonly at autopsy, and since

these do not come in contact with nerve roots they are symptomless. When the protrusion occurs in a postero-lateral direction it may press on the intra- or extra-dural portion of one or more nerve roots and when this occurs in the lower lumbar region sciatica results.

The herniated portion usually consists of a core of nucleus surrounded by a thin covering of annulus. But in some cases it may consist entirely of a fragmented portion of annulus.

PATHOGENESIS

Naffziger and his associates emphasize some interesting features in the mechanism of production of disc prolapse. In lifting a weight the lumbar region carries the brunt of the pressure attendant upon the use of the spinal column as a third class lever. By the use of force vectors they calculated that when one lifts a weight of fifty pounds the resultant pressure on a lower lumbar disc amounts to five hundred pounds. Also, when the spine is flexed the nucleus migrates dorsally increasing the tension on the posterior portion of the disc. Therefore, they attribute the frequency of posterior herniations to these three factors:

(1) Magnitude of the forces.
(2) Dorsal migration of the nucleus.
(3) Stress on the posterior portion of the disc.

To account for the frequency of unilateral lesions it is pointed out that very little rotation is permitted in the lumbar vertebrae. This limitation forces a certain amount of lateral bending in the lumbar region with migration of the nucleus to the contralateral side and production of a herniation on that side.

CLINICAL PICTURE

1. History. A frequent history obtained is that of a healthy man who feels something snap in his back while engaged in lifting a weight. He complains immediately of pain in his lower back and after a variable length of time the pain begins to radiate down his leg. This pain is increased by any movement that tends to stretch the sciatic nerve such as bending, sitting or walking. The patient may obtain some relief by lying down and adopting a certain posture in which there is a minimum of tension on the affected nerve.

In about half of the cases there is no history of injury and in these the onset may be more gradual with the patient suffering recurrent attacks of lumbago before the pain begins to radiate down the leg. Or the pain may be experienced first in the leg becoming progressively more severe. Whatever the mode of onset, pain is the outstanding feature of sciatica and it is the one that is most distressing to the patient.

Paraesthesias are common in the affected limb and a history of numbness and tingling, particularly in the foot, can usually be obtained.

In the chronic case the patient may complain of weakness on the affected side.

2. Physical Examination

(*a*) posture. There is often what is described as a "sciatic scoliosis." This is not a true lateral curvature but a list to one side and it probably represents an unconscious effort on the part of the patient to relieve pain. The inclination is generally away from the side of the sciatic pain.

The normal lumbar concavity is frequently absent or reversed, and there may be tilting upwards of the pelvis on the affected side.

(*b*) movements. All movements of the spine are restricted and extremes of

movement cause pain. Lateral bending to the side of the lesion is usually more painful than when bending away from the affected side.

(*c*) TENDERNESS. There is usually spasm and tenderness of the paravertebral muscles due to reflex guarding. The muscles supplied by the sciatic nerve are commonly tender and pressure over the nerve is painful.

(*d*) RADIATING PERCUSSION PAIN. Gentle percussion with a reflex hammer to the side of the midline at the level of the spinous processes of L4 and L5 may produce radiating sciatic pain. When positive this sign is strongly suggestive of a herniated disc. Also, one may be able to differentiate between L4 and L5 lesions by producing radiating pain at one level and not at the other.

(*e*) STRAIGHT LEG RAISING. Straight leg raising is invariably painful and the angle at which pain is produced may be a guide in following the progress of a case. With the straight leg raised, dorsiflexion of the foot at the ankle increases the tension on the sciatic nerve and also the pain (Laseque's sign). When this sign is positive it aids in differentiating sciatica from other painful lesions in the low back region.

(*f*) NEUROLOGICAL. As true sciatica is essentially due to a mechanical involvement of nerve roots one would expect to find both motor and sensory signs. However, these take some time to develop and they are not usually present in the early stages. In the well established case there is weakness and wasting in the affected limb and the ankle jerk may be diminished or absent. There is usually an area of cutaneous sensory impairment, and mapping out this may be of assistance in determining the level of the lesion.

3. SPECIAL EXAMINATION

(*a*) MYELOGRAPHY. This is mentioned largely to be discredited, at least as a routine procedure. Most workers today emphasize clinical diagnosis and deprecate injection of contrast media into the spinal canal. Lipiodol left in the spinal canal may cause meningeal irritation with aggravation of the sciatic pain. Furthermore, the results are not entirely reliable. The findings are frequently negative when a herniated disc is present and a positive result may be due to an artefact.

Myelography rarely may be indicated when there is strong clinical evidence of a herniated disc without clear cut neurological signs and it has been decided to operate. The radio-opaque material should then be removed at operation.

(*b*) RADIOGRAPHS. Lateral films of the lumber region commonly show absence of the normal lumbar lordosis. Narrowing of the interspace at the suspected level is supportive evidence of a herniated disc. This finding must be interpreted carefully, however, as the lumbosacral interspace is normally narrower than other disc spaces.

(*c*) LUMBAR PUNCTURE. If the protruding disc causes a partial subarachnoid block there will be increased protein in the spinal fluid and a positive Queckenstedt sign will be obtained. Examination of the spinal fluid is of value when spinal cord tumour enters into the differential diagnosis.

LEVEL OF THE LESION

FOURTH LUMBAR INTERSPACE

1. Radiating pain produced by percussion lateral to the fourth lumbar process.

2. Ankle jerk is usually normal but occasionally may be diminished.

3. Cutaneous sensory impairment in the fifth lumbar dermatome.

4. Weakness of anterior tibial group of muscles. (Weakness in dorsiflexion of great toe.)

Fifth Lumbar Interspace.

1. Radiating pain produced by percussion to the side of the fifth lumbar process.

2. Ankle jerk is diminished or absent.

3. Sensory impairment in the first sacral dermatome.

4. Weakness of the calf muscles (demonstrated by having the patient walk on toes.)

In some cases the neurological signs may point to involvement of both nerve roots. The explanation in some of these cases may be due to the fact that the first sacral root crosses the fourth and fifth lumbar discs, and a lesion of the fourth disc may involve this root. Double lesions involving both discs sometimes occur.

Rarely, the third lumbar disc herniates with involvement of the fourth lumbar nerve root.

DIFFERENTIAL DIAGNOSIS

1. Acute and chronic low back pain.
2. Root pressure from other causes.
3. Primary sciatic neuritis.
4. Osteo-arthritis of the hip.
5. Ankylosing spondylitis.
6. Acquired deformities.
7. Congenital deformities.
8. Trauma.
9. Malingering.

In considering the origin of low back pain one should think of the anatomical structures in that region, that is—muscles, ligaments and joints. It now generally is accepted that a "sciatica" may be due to lesions of these structures without direct compression of nerve roots. That is, pain arising in any of these structures may be referred along the course of the sciatic nerve, and this fact should be kept in mind when confronted with a sciatic distribution of pain. An acute "lumbago" may simulate an intervertebral disc lesion very closely and differentiation may be impossible in the early stages.

Chronic back pain due to a lesion of one of the above-mentioned structures can usually be differentiated from intervertebral disc lesions by the absence of neurological manifestations such as wasting. diminished reflexes and sensory changes.

Other causes of root pressure such as tumours of nerve roots, intra-pelvic carcinoma and collapse of vertebral bodies must be differentiated from disc lesions. The pain due to pressure of a tumour is usually not so severe as a true sciatica and it is often bilateral. A rectal examination should be performed in all cases to exclude intra-pelvic carcinoma. X-rays will usually reveal disease of the vertebral bodies.

A primary sciatic neuritis has not been established on a pathological basis, and if this lesion does occur it probably accounts for only a small percentage of the cases. It may be that a single attack of brief duration, in the absence of a history of injury, is due to a primary affection of the nerve.

Osteo-arthritis of the hip, frequently confused with sciatica, produces no neurological signs and causes limitation of movement at the hip.

In ankylosing spondylitis there is early evidence of arthritis in the sacro-iliac joints, and the sedimentation rate is usually elevated.

Acquired deformities such as scoliosis and kyphosis may provide a structural basis for low back pain.

Congenital defects such as spina-bifida, spondylolisthesis and an additional lumbar vertebra can be detected radiologically; these occasionally may be the cause of chronic low back pain.

In cases of trauma one should look for a fracture as a primary cause of back pain. Stereoscopic views should be taken to exclude fractures of the vertebral appendages which may not be seen in plain films.

If one suspects malingering it may be possible to demonstrate migratory tenderness.

TREATMENT

With the modern view as to the aetiology of sciatica the treatment has undergone radical change. Such procedures as stretching and injecting the sciatica nerve have now been abandoned in favour of a more logical approach to the problem.

The treatment of disc lesions falls into two categories: conservative and operative.

CONSERVATIVE. The most potent therapeutic weapon in the treatment of an acute attack is rest. A proportion of cases become symptom free following a period of absolute bed rest (4 to 6 weeks). Most workers agree that, in cases which relapse, the prognosis is better when the patient has been rested immediately and adequately.

Analgesics and warmth may be employed in the acute stage to ease the pain.

In the chronic or recurrent case of sciatica, if the pain is not too severe, it may be possible for the patient to remain ambulant. A physiotherapeutic regimen designed to strengthen back muscles, together with heat and massage to relieve muscle spasm, may enable the patient to continue to work. This should be combined with as much rest as the patient's occupation permits.

Some cases respond to manipulation, especially in the acute stage. It is believed that hyperextension widens the intervertebral space allowing the herniated portion of the disc to slip back into place.

OPERATIVE. The operative treatment consists of removing the herniated portion of the disc. In carefully selected cases the results obtained by a skilled neuro-surgeon are good. The majority of the patients are relieved of the root irritation although some residual low back pain may persist for a time.

As there is a large subjective element in sciatica and the operation is performed to relieve pain, the indications for surgical treatment have not been clearly established and each case must be evaluated separately.

The frequency and severity of attacks, the response to bed rest and the nature of the patient's occupation are factors which influence the decision to operate.

Contra-indications to operative treatment probably lie in the emotional make-up of the patient. Emotionally unstable patients usually do not respond as well to surgical treatment. Whether or not a patient receives workmen's or other compensation also seems to influence the results. Dandy quotes a series of 200 cases which were divided into two groups. In the first group compensation was a factor and 85 per cent of the results were poor. In the second group compensation was not a factor and 90 per cent of the results were good.[4] In some cases there is a large functional element. "Stocking" anaesthesias are not rare among patients with psychoneurotic tendencies and while there is often an organic basis for symptoms

these patients are probably not good candidates for surgery.

Following removal of the protrusion, a fusion of the fourth and fifth lumbar and first sacral vertebrae is sometimes performed. The usual indication for fusion is spinal instability which may be due to congenital anomalies or removal of a large portion of the annulus.

SUMMARY

1. New views regarding the aetiology of sciatica are considered.

2. Some of the conditions which may simulate sciatica are discussed.

3. The importance of early and adequate bed rest is stressed in the treatment.

4. Some features in the selection of patients for surgical treatment are considered.

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ABDOMINAL HERNIA

HELEN REESOR, 5T1

A HERNIA is the protrusion of any tissue of the body through a defect in the wall which normally confines it. Any tissue in the body therefore, which lies within some confine of skin, fascia, muscle or bone, is capable of herniating when given the opportunity.

Two factors must be present before a hernia will appear. Firstly, there must be a weakness in the wall which confines the tissue. Secondly, there must be some force exerted to expel the contents through the weakened wall. For example: an abdominal wall is weakened by every surgical incision, but an incisional hernia does not always develop. If, before healing of the wound is complete, the patient develops a cough which markedly increases the intra-abdominal pressure, then both factors necessary to hernia formation are present and an incisional hernia may occur.

Other factors which have a bearing on the incidence of hernia are: (1) heredity and (2) congenital factors. Twenty-five percent of patients with hernia give a family history of hernia. Hamilton Russell claims that herniation of abdominal viscera almost always occurs into a preformed sac of the peritoneum; this is especially true in indirect inguinal herniae which utilize the congenital pathway of the inguinal canal.

SITES OF HERNIAE

Commonest herniae are from the abdominal cavity; in order of incidence they are inguinal, femoral, umbilical, incisional and paraumbilical. Not unusual abdominal herniae are those due to divarication of the Recti, and fatty herniae of the linea alba. Very rarely hernia occurs in the gluteal, sciatic or lumbar region.

Herniation also occurs through the Diaphragm from the abdominal cavity. The term hernia can be applied to the bulging of brain tissue through a defect in the skull; of muscle through a defect in its fascial sheath; and of an intervertebral disc through a defect in its fibrocartilaginous ring.

This article will include discussion of the abdominal types of hernia only.

PATHOLOGY

Herniae consist of three parts: from within outwards they are the contents, the sac and the coverings.

In abdominal herniae the contents may include omentum, intestine, Meckel's diverticulum, bladder diverticulum, ovary, Fallopian tubes, testes, fluid and loose abdominal bodies (detached epiploical appendages). Part of the liver has also been seen in herniae.

The sac is usually a diverticulum of peritoneum with a narrow neck and a fundus which expands as the contents demand. The fundus is usually thin in a recent hernia; it may be thickened or cartilaginous in long-standing cases.

The coverings are those layers of skin and underlying tissue which are over the hernia and through which incision is made for surgical repair.

SYMPTOMS

The patient with a hernia does not seek medical attention until symptoms are sufficient to cause him distress, or until some examining board requires that his hernia be repaired.

A dragging sensation, or definite pain, may draw attention to a certain region. By observation the patient notes a swelling in that region. In the obese person the swelling may be obscured but the pain brings him to the doctor.

SIGNS

1. An impulse may be seen or felt when pressure is increased. An abdominal hernia will be accentuated when the person coughs or strains. It may be necessary to feel the impulse by inserting one's finger into the potential orifice, *e.g.*, the external inguinal ring.

2. Percussion may give some idea of the contents. Flatness may indicate muscle or omentum and tympany may indicate bowel.

CLINICAL CONDITIONS OF HERNIA

Reducible
Irreducible
Incarcerated
Strangulated

1. Reducible Hernia. It may disappear when the patient changes posture. Some of the abdominal herniae disappear on lying down; these are clinically reducible herniae. Whenever the patient is well enough for operative procedure these should be repaired surgically to avoid complications. The common methods of repair are as follows.

(*a*) Herniotomy: removal of the sac.

(*b*) Herniorrhaphy: removal of the sac with repair of structures around the orifice.

(*c*) Hernioplasty: similar to herniorrhaphy but fascial graft or suture is used to repair the orifice.

2. Irreducible Hernia. This type cannot be reduced clinically, but there are no complicating signs present. Usually there are adhesions of the contents to the sac which prevent reduction. Surgical repair is advised (as in 1. above).

3. Incarceration is an early stage of strangulation. It is difficult to diagnose clinically and often is proven to be early strangulation when incised.

The immediate application of cold (ice bags) to the incarcerated hernia is advised. The site should be elevated, and a sedative should be given to relax muscle spasm. With this treatment reduction often becomes possible.

4. Strangulation. The blood supply is impaired and gangrene has developed already or is imminent. The signs of strangulation are pain, lack of impulse on coughing and local tenseness. If strangulation is not relieved, bacterial invasion of the contents will lead to abcess formation in the sac and peritonitis.

Much more important than infection, is intestinal obstruction when the strangulated hernia contains small or large bowel.

Surgical repair of strangulation is urgent. At operation the sac is opened, the neck of the sac is divided, and the contents are examined to determine whether they should be returned to the body cavity or not.

(*a*) Healthy tissue is returned.

(*b*) Necrotic tissue or gangrenous contents are removed. (In the case of bowel, an end to end anastomosis is required to restore continuity.)

(*c*) Doubtful tissue (especially bowel) may be wrapped in hot, moist, saline dressing for five minutes or longer; if at the end of this treatment the tissue shows signs that there is vascular supply to the part then it is replaced. Pulsation of vessels and return of peristaltic waves to the part indicate that the tissue is viable. If the tissue is avascular then it must be removed.

(*d*) In the very ill patient temporary relief may be given by opening the sac and exteriorizing the gangrenous contents. Supportive treatment is given until the patient is well enough to undergo surgical repair. If the lesion is in the gastro-intestinal tract, the exposed intestine may act as a temporary enterostomy until the patient is well enough for surgical resection and anastomosis.

Increased Intra-abdominal Pressure

Muscular strain associated with dysuria, difficult defaecation, and chronic cough are the commonest causes leading to abdominal herniae.

In manual labourers sudden muscular strain associated with the person's work may give rise to a hernia; many such herniae are considered as reasonable claim for Workmen's Compensation.

In females, the pressure of pregnancy, large ovarian cysts or fibroids may lead to herniation of abdominal contents.

TYPES OF HERNIAE

1. Inguinal

(*a*) INDIRECT INGUINAL HERNIA. These follow the path of an unobliterated funicular process. They tend to appear at a relatively young age. The distance down the peritoneal tube that the contents descend varies; they may just enter the inguinal canal and not pass through the external ring, or they may descend into the scrotum to produce a very large hernia.

The neck of the inguinal hernia always lies above and medial to the pubic tubercle. A finger inserted through the external inguinal ring will detect a fullness in the canal.

Diagnosis may be confused with femoral hernia, undescended testis, hydrocele of cord (or of canal of Nück), or cord lipoma. To differentiate the hydroceles it will be useful to transilluminate the swelling.

(*b*) DIRECT INGUINAL HERNIA. This develops most frequently in older patients, through the weakened posterior wall of the inguinal canal. The breakthrough is always in Hesselbach's triangle which is bounded by the lateral edge of the Rectus muscle medially, Poupart's ligament below, and the inferior epigastric artery laterally. If the pulsation of the artery can be felt in the lateral border of the ring, one may be sure that the hernia is of the direct inguinal variety.

The little finger inserted through the enlarged external inguinal ring encounters no resistance posteriorly and seems to extend straight back into the abdomen instead of obliquely upward along the canal as in the direct type.

(*c*) SLIDING INGUINAL HERNIA (*Hernie-en-glissade*). In this type the posterior wall of the sac is not peritoneum but the caecum (on the right) or the pelvic colon (on the left). This condition results when the posterior parietal peritoneum slips downward. These herniae are large and have been irreducible for years.

(*d*) INTERSTITIAL INGUINAL HERNIA. In the presence of a diverticulum of a sac in the inguinal region, the contents may pass into the outpouching. The contents come to rest wherever the diverticulum has penetrated—between External Oblique aponeurosis and Internal Oblique, or between the conjoined muscle and the transversalis fascia. Predisposing factors are maldescended testis, superimposition of the rings, or absence of Cremaster.

2. Femoral

(*a*) The femoral canal is only partially occupied by lymph glands and fat. These can be readily displaced by abdominal contents which pass behind Poupart's ligament, through the femoral ring into the canal pushing peritoneum ahead of them. At the saphenous opening, the sac then readily turns forward out of the canal. Surgical repair of the femoral ring has the added hazards of the femoral vein on the lateral side and the possibility of the bladder being drawn in with the medial layer of peritoneum.

Although these herniae occur twice as commonly in females as in males they are still not as common as inguinal herniae in women. Their maximum incidence is in the third to fifth decades.

When these herniae are large, they tend to bulge upwards over Poupart's ligament and occupy the inguinal region. However, examination of the neck of a femoral hernia will prove that it originates below and lateral to the pubic tubercle.

This hernia should be differentiated from inguinal hernia, Psoas abscess or bursa, varix of saphenous vein, obturator hernia, hydrocele of femoral sac, lipoma, femoral aneurysm and enlarged inguinal lymph glands.

(*b*) richter's hernia. This is a special sort of hernia; only one border of a loop of the intestine is caught while the rest of the cross section of the bowel is free so that the lumen is left open and functioning. This cherry-like portion protrudes very much like a swollen lymph node (and can be mistaken for that). Impaired circulation leads to gangrene in that piece of the wall of the intestine while the patient shows no signs of obstruction. Immediate surgery is required. Taxis (reduction by manipulation) should not be attempted for fear of perforating the bowel.

3. Umbilical

(*a*) congenital umbilical hernia. The commonest cause of this condition is the failure of the umbilical hiatus to heal soundly after division of the umbilical cord. Every time the baby cries, abdominal contents push a sac of peritoneum out through the hiatus under the skin. Keeping the hiatus obliterated constantly with strapping may result in its healing. If this is unsuccessful surgery ultimately may be required.

A more severe sort of congenital umbilical hernia is "exomphalos". Skin also is defective and the abdominal viscera are covered only by the delicate amnion. These are rare; death is inevitable from peritonitis unless surgical repair is successfully completed a few hours after birth.

(*b*) infantile umbilical hernia. This usually occurs by the age of three. Like all scar tissue, umbilical scar will allow herniation if intra-abdominal pressure is raised while the scar is weak. In children, cough, or tuberculous peritonitis may be causes which must be treated before surgical repair will be effective.

(*c*) para-umbilical hernia. This is the adult form of umbilical hernia. The contents protude through a weakness in the linea alba, most usually above the scar. These are more common in women than in men; pregnancy and obesity are factors which cause weakness or flabbiness in this region.

4. Ventral Hernia.

Any hernia which occurs through the anterior abdominal wall in a region other

than the inguinal, femoral or umbilical, is called a "ventral hernia".

(*a*) EPIGASTRIC HERNIA. It occurs usually in manual workers between the ages of thirty and forty. A sudden severe strain of the Recti may tear the aponeurosis of the linea alba; through the weakened part knobs of fatty tissue protrude. Surgical repair is advised only if the lesion gives rise to local pain, nausea, and vomiting.

(*b*) DIVARICATION OF THE RECTI. This occurs in infants and in multiparous women. In infants it occurs above the umbilicus and tends to heal spontaneously. In older women, it occurs below the umbilicus and is best treated by an abdominal belt.

(*c*) INCISIONAL HERNIA. Any abdominal scar may become the site of an incisional hernia. Poor closure of the wound, infection of the wound, or strain on the wound in the immediate postoperative period as by distension, vomiting, or chronic cough are the common causes. Repair by hernioplasty (fascial sutures) may become necessary if the hernial ring is small and contents recurrently become incarcerated.

5. DIAPHRAGMATIC.

(*a*) CONGENITAL DIAPHRAGMATIC HERNIA is the commonest sort. This seldom gives rise to symptoms. After barium sulphate meal the outline of the stomach may be seen by X-rays to extend into the thoracic cavity. It, or any part of the gastro-intestinal tract, may gain entrance to the thorax through the oesophageal orifice, or through a hiatus in the Diaphragm.

(*b*) TRAUMATIC DIAPHRAGMATIC HERNIA may occur following war wounds, motor accidents, etc.

When symptoms appear which are associated with the presence of a diaphragmatic hernia (respiratory, cardiac, or gastric embarrassment) relief may be obtained by (1) paralysing that side of the Diaphragm or (2) by repairing the hiatus; to close the defect the thoracic approach is often used.

6. RARER TYPES OF HERNIA.

(*a*) LUMBAR HERNIA may occur through the superior lumbar triangle (bounded by Erector Spinae, Internal Oblique, and the twelfth rib). They also occur through the triangle of Petit (bounded by the Latissimus Dorsi, External Oblique and iliac crest). These must be differentiated from a phantom hernia which occurs in anterior poliomyelitis due to paralysis of the abdominal muscles when innervation of those muscles is impaired.

(*b*) GLUTEAL HERNIA passes on either side of the Pyriformis through the greater sciatic notch.

(*c*) OBTURATOR HERNIA passes through the obturator foramen of the pelvic girdle.

(*d*) PERINEAL HERNIA occurs into the labium majus or into the ischio-rectal fossa. This hernia is reducible and does not usually strangulate.

SUMMARY

A brief outline of types of abdominal herniae is given. The sites of occurrence are described, and some indication of the incidence and type of treatment is suggested.

ACKNOWLEDGEMENT

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TRAUMATIC INTRACRANIAL HAEMORRHAGE

ARTHUR J. HUDSON, 5T0

THE PATIENT WITH HEAD INJURY may quickly succumb to the effects of extensive brain contusion and laceration or survive days or even weeks to die untreated from the effects of an expanding intracranial lesion. Little can be done in the former case, but in the latter a diagnosis and localization of the site of intracranial haemorrhage may afford opportunity for immediate and effective treatment. To this end an examination in three parts is outlined below, followed by a discussion of the characteristics of the specific forms of traumatic intracranial haemorrhage.

The presence of signs immediately following head injury are usually due to brain damage, whereas those which are delayed in onset are generally the result of an enlarging blood clot. The pressure of an expanding mass within the cranium will cause both progressive damage to the surrounding tissue and a steady displacement of the brain with indirect focal pressure upon other neural structures. As each part becomes subject to this focal pressure it will become clinically manifest by disordered function of an associated part of the body.

EXAMINATION OF HEAD INJURY

1. LEVEL OF CONSCIOUSNESS

It is not uncommon to hear of a "lucid interval" occurring in connection with a case of head injury. This refers to the period of consciousness occurring between two episodes of unconsciousness. The first episode is due to the immediate effects of trauma, called concussion, and the second frequently is due to an expanding intracranial lesion, but is not necessarily so. Whether increased intracranial pressure is responsible for a return to unconsciousness or not may be determined, with the aid of other findings to be discussed, by the progress of the unconscious state. It is of value, therefore, to have a knowledge of "assessing" levels and to keep a record of these.

(*a*) FULL CONSCIOUSNESS.

(*b*) CONFUSION: *Mild.* Coherent responses to questions but memory grossly impaired, drowsy.

Severe. Great difficulty in obtaining responses to even simple demands, extreme drowsiness.

(*c*) DELIRIUM: Unresponsi veto questions, restless and resistive.

(*d*) STUPOR: Mute, responds only to painful stimuli. Reflexes are present but perhaps diminished.

(*e*) COMA: A profound state, with absence of reflexes, no response to painful stimuli, and even perhaps temporary cessation of respiration.

2. CHANGES IN THE VITAL FUNCTIONS

The state of the vital functions is determined by the pulse, blood pressure, respiratory rate and temperature, which should be recorded at half hourly intervals. The increased pressure of an expanding intracranial lesion causes a progressive loss of consciousness which can be detected as outlined above. However, when the patient reaches coma, alterations in vital functions occur as the pressure from a haematoma becomes extreme. Compression of the medullary veins is believed to be responsible for these changes and the picture is similar to that seen in asphyxia. The pulse may

be observed to slow and the blood pressure to rise. This is seen particularly well in the sharp rise of blood pressure occurring with a rapidly expanding extradural haematoma. If unrelieved, the pressure becomes so severe that a fall in blood pressure with a rise in pulse rate may follow. The pulse will become weaker and the blood pressure will disappear with the approach of death.

Simultaneously with these changes alterations in respiratory function, presumably from the same cause, will develop. The respirations will be moderately deep and regular and as the pressure becomes severe they will tend to become irregular and stertorous. Periodic or Cheyne-Stokes respirations may result shortly before death.

Temperature is of little value for, if elevated, it indicates irreparable brain damage. It is a terminal finding, usually.

3. Special Signs of Intracranial Haemorrhage

There are certain signs of intracranial haemorrhage which not only signify the presence of lesion but often enable its localization.

(*a*) HAEMORRHAGE AND FRACTURE: Blood or spinal fluid in the ear, nose, pharynx, or subconjunctival space may indicate fracture into the cranial fossae (anterior and middle). Radiological examination may detect fracture or a pineal shift.

(*b*) EYES: i. The pupil is frequently dilated on the same side as the cerebral compression but this is of localizing value only when marked. As the pressure increases the pupil becomes fixed and insensitive, at which time the pupil of the opposite eye may be large but as yet unfixed.

ii. Oculomotor palsy is valuable but uncommon. It occurs on the homolateral side usually. It is believed that basilar pressure is responsible for this and pupillary changes when these findings are homolateral.

ii. Fourth and Sixth nerve findings are rare.

iv. Papilloedema is a rare finding except in prolonged raised intracranial pressure. Engorgement of the retinal veins is a more reliable sign of increased pressure.

(*c*) CONVULSIVE SEIZURES: Jacksonian seizures are of valuable localizing significance in intracranial damage. Presumably they are a focal, irritative, cortical phenomenon.

(*d*) HEMIPLEGIA: Since pressure on one hemisphere may press the opposite cerebral peduncle against the tentorium cerebelli, it is not surprising that hemiplegia may be on the homolateral or contralateral side to intracranial haematoma. It is a sign of severe pressure. Weakness precedes definite paralysis when due to an expanding lesion.

(*e*) CEREBROSPINAL FLUID: The pressure is usually elevated but is not related to consciousness or blood pressure. Raised pressure is a sign of intracranial pathology and not the cause. It may be clear, xanthochromic or bloody even in proven extradural haemorrhage. Lumbar puncture is performed with caution.

(*f*) OPISTHOTONUS AND KERNIG'S SIGN: Meningeal irritation usually accompanies gross subarachnoid haemorrhage, evidence of which may be gained on lumbar or cisternal puncture.

(*g*) VOMITING: Raised intracranial, pressure may cause forceful vomiting not preceded by nausea. This is said to be due to increased excitability of the medullary centre.

(*h*) ELECTROENCEPHALOGRAPHY: Localization may be possible.

(*i*) AIR STUDIES: These are ill advised, since "coning" may result. Replacing spinal fluid with air or oxygen may define an extradural or subdural haematoma. Ventriculograms are impractical since the necessary burr holes may uncover the haematoma, if present.

(*j*) HEADACHES: In a conscious patient, raised intracranial pressure will cause generalized headache. On the other hand localized headache is said to often overlie particularly a subacute and chronic subdural haematoma. (Gurdjian and Webster.)

FORMS OF TRAUMATIC INTRACRANIAL HAEMORRHAGE

1. Extradural haematoma.
2. Subdural haematoma (*a*) acute, (*b*) subacute, (*c*) chronic.
3. Subarachnoid haemorrhage.
4. Intraparenchymatous (*a*) petechial (*b*) massive.

1. EXTRADURAL HAEMATOMA

PATHOGENESIS: An extradural haematoma is formed almost invariably in association with skull fracture. The middle meningeal artery or one or more of its branches is most often damaged, causing a collection of blood to form between the dura and the inner table of the skull. The venous sinuses are responsible occasionally and one author drew attention to the occipital emissary vein in depressed fractures.

The size and rapidity of formation of a blood clot depends upon the size of the vessel torn and the age of the patient. The dura becomes very adherent to the skull in older patients and its separation would be more difficult. In infants and children, on the other hand, the dura is very loosely adherent but the vessels, as well, are not so fixed since they lie in shallow grooves. In this age group a fracture is less likely to be followed by tearing of a large vessel.

Injury to the middle meningeal trunk, deep in the middle cranial fossa, is serious, since the basal structures, more vital to life, may be damaged. The haematoma in this case develops rapidly.

SIGNS AND SYMPTOMS: "Extradural haemorrhage . . . is an acute process and usually comes to the attention of a physician in a matter of hours" (King). However, diagnosis may not be evident for perhaps seven or eight days. A small clot may form as a result of damage to very small vessels and never be recognized.

A so-called pathognomonic "lucid interval" has often been outlined for extradural haematomata which unfortunately is frequently just as typical of other intracranial injuries. Its occurrence is unquestionably frequent, but it is not diagnostic. Very often full consciousness does not occur, although confusion or delirium may be reached only to have a patient return to stupor and coma. In a series of 35 cases (Gurdjian & Webster) 35% were reported as becoming fully conscious while the same number remained unconscious. About twenty-three percent became drowsy and disorientated before again becoming unconscious.

Since expansion is generally rapid the resulting physiological events are rapid and a sharp rise in blood pressure with a marked fall in pulse to 45-60 may aid in differentiation from the usual more slowly expanding subdural harmorrhage. A blood pressure rise is less frequently seen in the latter, since the rate of rise of intracranial pressure is gradual.

Pupillary changes, ocular palsies, Jacksonian convulsions and hemiparesis and paralysis have already been discussed, and need not be reiterated. Differenti-

ation from a subdural haematoma on the basis of these signs may not be possible.

The cerebrospinal fluid may be clear, xanthochromic or bloody, depending upon a damage to the cortical pial vessels. Gurdjian and Webster in their series noted only 3% clear.

TREATMENT: Subtemporal decompression on the side of the lesion is performed. Bleeding points are controlled (ligation) and care taken not to overlook a subdural haematoma. Adequate and timely treatment may be rewarded by full recovery although hemiplegia may have been present.

2. Acute Subdural Haematoma

PATHOGENESIS: Acute haematomata are usually considered to be that group in which the clot, when removed, consists of fairly fresh blood (currant jelly or reddish fluid). Actually they are more clearly visualized clinically as those cases with a history of severe trauma, including skull fracture, which are almost invariably rendered unconscious and may or may not have a "lucid interval." In this group may be recorded all cases requiring operation up to about seven days following trauma. In such a group reported by Echlin, half required operation within twenty-four hours, almost all of whom died from extensive brain injury, the haematoma being an almost incidental complication.

Tearing of the pial vessels with the accumulation of blood or blood and spinal fluid in the subdural space through tears in the pia-arachnoid is probably most often responsible. Tearing of the cortical veins traversing the subdural space to enter the venous sinuses also may occur.

The clot is usually quite extensive and unlike an extradural haematoma it need not lie beneath the site of fracture but may be "contre-coup." One author records a frequent fronto-parieto-temporal distribution, often bilateral, due to a sudden cessation of forward movement of the head and abutment of the frontal and temporal lobes against the irregular surfaces of the bony encasement.

SIGNS AND SYMPTOMS: The signs of parenchymal damage may predominate the picture. Differentiation from extradural haemorrhage will otherwise likely be impossible. Any of the signs of intracranial haemorrhage previously discussed may be present.

TREATMENT: See chronic haematomata.

3. Subacute and Chronic Subdural Haematomata

PATHOGENESIS: In these two groups the progressive signs and symptoms are due to a clot which presumably expands through the process of osmosis. Monro discusses three types of subdural haematomata in general and states that the "osmotic" type must be a combination of blood and spinal fluid. Pure blood haematomata tend to organize and may expand only by further haemorrhage. These may persist a lifetime. The third type consist of cerebrospinal fluid only, and are therefore clear (hygroma). In the "osmotic" form the fluid may range from a dark coffee colour to almost clear. Subacute cases are those requiring operation between 7 and 30 days, more or less, using this group as a carry over from acute to chronic cases.

A history of trauma immediately followed by unconsciousness is almost invariably recorded in subacute cases whereas a history of trauma alone, or even lacking this, is usual in chronic haematomata. It appears, therefore, that a subacute haematoma is merely an acute form lacking the extensive cerebral injury. Undoubtedly this is also true of chronic cases, but, in view of a frequent

history of very mild trauma, a particular mechanism seems responsible. In this regard King notes tearing of the venous trunks which traverse the subdural space by propulsion forward of the brain in the cranial vault. This occurs in the other forms but in this group unusually short trunks (congenital) may readily predispose to rupture.

SIGNS AND SYMPTOMS: A gradual onset is almost pathognomonic. To corroborate this feature it will be noted that the course of headache and drowsiness is fluctuating but progressive. Fluctuation in the relative size of the pupils may be observed in many cases.

Of importance is the complaint of a headache which has been reported to frequently overlie the clot. Gurdjian and Webster, in 65 cases, noted homolateral headache in 42 and generalized headache in 11.

The cerebrospinal fluid pressure may be over 300 and is almost always elevated. This refers to clinically defined cases.

The blood pressure and pulse are usually normal. Papilloedema may be present. The signs of focal pressure discussed elsewhere may be seen also, *e.g.*, hemiparesis.

TREATMENT: Both hemispheric surfaces should be explored. The skull should be trephined at the fronto-parietal junction two inches from the midline and if found a subtemporal decompression should be done. This is also the treatment in acute cases.

4. Subarachnoid Haemorrhage

Cerebral contusion and laceration is the usual cause of subarachnoid haemorrhage. It is the most common form of traumatic intracranial haemorrhage but rarely if ever does it reach the proportions of spontaneous rupture of a cerebral artery (aneurysm). Parenchymal injury is the outstanding feature.

5. Intraparenchymatous Haemorrhage

Following a blow on the head a patient may suffer merely concussion which is characterized by unconsciousness with no other complications.

A more severe blow may cause cerebral oedema and congestion; the resultant swelling of the brain during and after unconsciousness may cause nausea, dizziness, headache, loss of memory and inability to concentrate. Petechial haemorrhage occurs, due to rupture of small veins and capillaries, which may cause some permanent damage but rarely causes death. The intracranial pressure is elevated frequently, but the cerebrospinal fluid will always be clear. Hemiplegia and convulsions can occur.

Contusion and especially laceration are accompanied by serious parenchymal damage. They are associated with oedema and congestion when present, as well as with subcortical haemorrhage. Unconsciousness (coma) following severe trauma may last days. Respiratory irregularity, sudden dilatation of the pupils and a rise in temperature and pulse heralds death. Headache, nausea and vomiting, and retrograde amnesia occur with recovery of consciousness. The intracranial pressure is high, with blood in the cerebrospinal fluid. Residual damage varies and may be extensive. Signs are present immediately or very shortly following injury.

TREATMENT: Non-operative. Lumbar drainage to relieve pressure is performed. Dehydration measures are of questionable value.

SUMMARY

The subject of traumatic intracranial haemorrhage has been presented, with the signs of intracranial haemorrhage discussed first, to avoid needless reiteration in the descriptions of the specific forms of haemorrhage. The highlights in clinical findings are noted with, unfortunately, the necessary omission of corroborative detail; for example, the changes in reflexes associated with hemiparesis. Treatment is dealt with only summarily since the entire problem is essentially neurosurgical.

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PHYSIOTHERAPY

SHEILA RIDDEL*

REHABILITATION is a comparatively new word, but the principle behind a rehabilitation scheme was recognized by Plato two thousand years ago when he stated, "there are physicians for the body, and physicians for the soul, and yet the two are one and indivisible." Recent recognition of the fact that a patient is an ill *person*, whose mental processes and physical well-being are interdependent, has resulted in prominence of the term, "psychosomatic medicine." It is felt that the role of the physiotherapist in this concept should be clarified.

In a society which has an increasing life-expectancy and an increasing percentage of old persons, it is an economic necessity to return to usefulness all temporarily or partially incapacitated persons as quickly and as completely as possible. To effect maximum recovery of the patient, a variety of services work as a team directed by a medical practitioner. The physical therapist, the occupational therapist, the social worker, the x-ray and laboratory technicians, and the psychologist are all members of this group.

The part that the physical therapist can take in the program for the patient depends on: (*a*) her medical and technical knowledge; (*b*) the orders she receives from the doctor; (*c*) her ability to carry out these orders efficiently.

To further her general medical knowledge and to increase her success in treating individual patients it is earnestly recommended that the therapist have access to histories and x-rays before she treats a patient. To insure adequate treatment and good results, it is helpful to doctor, patient, and therapist alike, if the therapist attends rounds with the physician. She then is able to report progress, discuss difficulties, and receive instructions for future treatments. Although nearly all therapists are busy with scheduled treatments, it is felt that time spent attending rounds is worth much to the patients. If, however, it is impossible for her to be present for verbal consultation, a special sheet on each patient's chart for doctors' orders concerning physical therapy and daily progress notes by the therapist is helpful. These sheets form a basis for research data from which the benefits of various physical treatments may be estimated—such data has been sadly lacking in the past.

The orders which the therapist receives should be as explicit and as detailed as possible, at least until she and the physician have evolved a routine method of treatment for a given disability. Armed with her training, a case history, and her orders, the therapist should be able to plan her treatments most satisfactorily.

Treatments may be local or general. Local treatment, directed to the disabled part, may include the use of any of the physical modalities such as heat, massage, and exercise. The objective of local treatment is return of function (*i.e. controlled* movement) in the disabled part. The part must have rigid bone, free joint movement, strong muscle, and an intact nervous system to function normally. Although all parts are not intact, or free to function normally, it is essential *that all non-affected*

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parts be kept in good working condition. For example, if a patient is taught to practise quadriceps contractions, while immobilized following a menisectomy, then, on removal of the restriction of movement, the muscle is in good condition to control movement of the knee-joint and to overcome stiffness. To be effective, local treatment must be started early before disuse has resulted in atrophied muscles and stiff joints. Local treatment also is valuable to the patient for it prevents development of an over-protective attitude toward the disabled part and it prepares, mentally and physically, for re-introducing the part to activities of the whole organism, when the doctor allows this. It is the therapist's job to explicitly instruct the disabled patient regarding the exact amount of movement to be attempted; she can save the doctor valuable time by being ordered to do so.

General treatment applies mainly to bed-patients. Any patient who is bed-ridden for more than a few days needs general treatment before being allowed up. It is unreasonable, I think, to expect a patient, who has been inactive for some time, to enjoy, or be reasonably efficient in, the erect position. Muscles which are inactive waste and weaken, joints which are not moved stiffen, and circulation slows if the venous return is impaired by decreased muscular contraction. The therapist, by giving a short, simple scheme of exercises for all non-affected parts, and breathing exercises, can hasten the patient's return to normal activity. General treatments, I believe, can shorten greatly the convalescent period of many illnesses.

It will be observed that the emphasis of this outline is on active exercise. This is so because it is unreasonable to expect to re-educate the patient in the use of a part unless he can practise. In the past, physical therapy commonly consisted of massage, passive manipulation and heat treatments, which may be why many treatments left much to be desired. *A therapist is primarily a teacher of normal function* and, although she uses the above-mentioned modalities, they will not replace, in themselves, active movement.

At the beginning of this paper the interdependence of mind and body was mentioned. It is essential that the therapist recognize this, since to teach function she must approach each patient in a way which will ensure co-operation. She must have the co-operation of the patient because, while the method is her's to teach, its success rests solely on the patient's ability and desire to recover.

THE MERCURIAL DIURETICS

J. F. H. STEWART, B.A., L.Th., 5T0

ALTHOUGH A COMPOUND OF MERCURY (mercurous chloride) was used as a diuretic as early as the sixteenth century, it was Saxl and Heilig[1] who introduced the mercurial diuretics into the field of modern therapeutics. In 1920 they published the results of their treatment of a case of luetic aortic insufficiency with œdema (and some other non-nephritic œdematous patients) using novasurol (merbaphen), an organic compound containing mercury.

COMMONLY USED MERCURIAL DIURETICS

The mercurial diuretics are organic compounds containing mercury in an ionizable form that are used to "promote the formation of urine."[2] Those commonly employed are:

MERCUROPHYLLINE INJECTION (U.S.P.) (T.N. Mercupurin, Mercuzanthin, Novurit). Mercurophylline is mercurin plus theophylline.

MERSALYL AND THEOPHYLLINE INJECTION (U.S.P.).

INJECTION OF MERSALYL (B.P.) (T.N. Solution Salyrgan-Theophylline).

MERALLURIDE SODIUM SOLUTION (N.N.R.) (T.N. Mercuhydrin Sodium Solution).

Each of the aforementioned compounds contains about 40 mg. of mercury per cc.; they are all available in 1 and 2 cc. ampules.

ENTERIC COATED TABLETS MERCUZANTHIN (N.N.R.).

ENTERIC TABLETS SALYRGAN THEOPHYLLINE (N.N.R.).

Each of these tablets contains about 30 mg. of mercury, and is intended for oral use.

MERCUPURIN SUPPOSITORIES (Campbell Products Incorporated, New York); Salyrgan-Theophylline Suppositories (Winthrop): contain about 0.5 Gm. of the mercurial salt in cocoa butter. Each suppository contains about 200 mg. of mercury.

THIOMERIN (not in N.N.R. or B.P.), a compound of mercurin and thioglycollic acid, 1 cc. of which contains about 40 mg. of mercury, was introduced into the medical literature as M T 6 in 1947,[3] and is manufactured by Campbell Products Incorporated, New York.

SITE AND MODE OF ACTION

That the kidney itself is the main, if not the only site of action of the mercurial diuretics was finally established by Govaerts,[4] in 1928, in his classic experiments on dogs, and confirmed by Bartram[5] in 1932. That their effect is on the absorptive action of the kidney tubules, was suggested by Schmitz[6] in 1932, and demonstrated by Walker[7] in 1938, working with rabbits and dogs, and he also showed that mersalyl does not appreciably alter the other two factors influencing the volume of urine excreted, namely the renal blood flow and the glomerular filtration rate; and, according to Hermann and Decherd,[8] this also is true in man. In rats, however, the glomerular filtration rate also is increased.[9]

In all probability it is the liberation of mercury ions from their organic combination within the body that causes the diuresis, for compounds containing ionizable mercury have a greatly superior diuretic effect when compared with that of compounds of unionizable mercury.[10]

How the mercurial diuretics probably act upon the kidney tubules may be inferred from the experiments of Farah and Maresh.[11] They observed that British anti-Lewisite (BAL) counteracted the action of mersalyl when injected into rabbits and dogs in the molecular equivalent ratio in which BAL counteracts the action of mercury in other situations. Since it has been shown that BAL nullifies the activity of mercury by forming a compound with mercury on its sulfhydryl groups, they conclude that the mercurial diuretics inactivate one or more sulfhydryl-containing enzyme systems in the kidney tubules that are responsible, directly or indirectly, for the reabsorption of water and sodium chloride from the tubule lumina. Duggan and Pitts[12] have shown that the mercuric ions act on the cells of the distal (but not the proximal) convoluted tubules by demonstrating that 15 to 20 per cent of the sodium in the glomerular filtrate (in dogs) is reabsorbed in these tubules, and that the maximum percentage of sodium in the glomerular filtrate that can be prevented from being reabsorbed by a mercurial diuretic is 15 to 20 per cent also.

The sequence of events occurring after the injection of a mercurial diuretic is as follows. There is a transient reduction in renal blood flow, probably due to a transient renal vasoconstriction,[11] and so a transient reduction in kidney volume; an initial decrease in urine flow,[13] which is followed by an increased excretion of water sodium chloride, potassium and calcium. In the urine excreted, the specific gravity does not differ measurably from that of normal urine, its concentrations of sodium, potassium, and calcium are similar to those in normal urine, but its concentration of chloride is greatly in excess of that found in normal urine.[13]

A loss of body weight (3 - 6 per cent), a fall in plasma volume (15 - 25 per cent)[14 15], a fall in serum chlorides, a rise in serum bicarbonate, and little change in the serum sodium and calcium [16a] have been reported following mercurial diuresis in healthy men. Diuresis is followed by a compensatory retention of water and sodium chloride.[13]

In patients with cardiac failure, the injection of a mercurial diuretic results in considerable improvement, not only through relief of dyspnœa and the other effects of œdema, but also because of a reduction in their high venous pressure.[17] (The reduction is proportional to the diuresis.)

Doubling the dose of mersalyl (from 1 to 2 cc.) doubles the duration of the diuresis, triples the volume of urine and amount of sodium chloride excreted in healthy men.[13] In patients with cardiac failure, however, giving two 1 cc. doses in one week results in a 20 per cent greater total diuresis than is obtained with one 2 cc. dose, and is more comfortable for, and less dangerous to, the patient.[18]

Ammonium chloride, apparently as the result of its acidifying action, works synergistically with the mercurial diuretics, the two together giving a response greater than that produced by both acting singly. The chloride excretion is proportionately greater than that of water[16b *and* 18].

The action of theophylline when used in conjunction with a mercurial diuretic is: to increase the absorption[19] of the mercury compound and prevent its deposition[20] when it is injected intramuscularly, and so decrease the local toxic reaction, accomplished in some measure

by reducing the pH of the mercury compound, the absorption of which decreases as the pH increases[20]; to lower the acute intravenous toxicity[21]; to increase the maximum rate of urinary excretion and the amount of diuresis[22]; and to increase the rate of excretion of mercury by all methods of administration.[23] These actions of theophylline are probably the result of its chemical combination with the mercury compound.[19]

There are no significant differences in the diuretic efficiency of the various mercurial diuretics without theophylline[10] (including Thiomerin[24]), or among those combined with theophylline, or in the same drug injected intravenously and intramuscularly.[25]

In Thiomerin, the dissociation of mercury ions is very largely prevented before the substance reaches the kidneys by the mercaptide type of chemical union between its two components, which forms a complex that is more stable than that combining one of the mercury compounds and theophylline.[26]

The diuresis resulting from the use of a mercurial diuretic begins about 1 to 3 hours after a injection, is greatest about $1\frac{1}{2}$ to 4 hours after injection, and ceases in about 12 to 24 hours.[16b] The action, however, when used on patients not in normal health is variable: they may have no resulting action; they may act only after several injections; there may be decreasing effectiveness with successive doses; or they may give a good response with repeated injections for months or years.[2]

TOXICITY

The medical literature of the present decade contains a number of reports of severe or fatal reactions following the use of mercurial diuretics (43 cases of sudden death before July, 1946,[27] and a number of instances of other toxic reactions). Fatal reactions have followed only intravenous injections, almost always of 2 cc. or more.

These reactions are of three main types: (*a*) reactions at the site of injection; (*b*) those directly related to the drug used (either the mercuric or the organic portion thereof), and (*c*) those related to the associated diuresis.

Reactions at the Site of Injection

A local slough or abscess may form at the site of injection of all of the mercurial diurectics[2c] except Thiomerin[28] (from which almost no mercury is released in this location[29]), and burning pain and muscular cramps, which appear in 1 to 3 minutes and last for 5 minutes to 4 days, also may occur there.[25] (Thiomerin given subcutaneously, however, occasionally gives local soreness and nodulation[29].) Mercurin is not as toxic as mersalyl[20] (nor is mercurophylline as toxic as mersalyl with theophylline), and meralluride gives fewer reactions than mercurophylline.[25]

Reactions Directly Related to the Drug Used

In the fatal cases, toxicity is manifested by ventricular fibrillation. Electrocardiographic changes indicative of disturbed ventricular activity commence with the completion of intravenous injection of a mercurial diuretic; they merge into ventricular fibrillation[30] with consequent death in five or ten minutes from cardiac arrest, or respiratory failure secondary to cardiac irregularity.[21] Very similar electrocardiographic changes in dogs[27] suggest strongly that in man also the mercuric ion acts directly on the cardiac musculature in these patients.

In the immediate non-fatal reactions (also the result of the action of mercuric ions on heart muscle, in all probability[31]) the patient, 2 or 3 minutes after an injection, has some of the following symptoms: a feeling of apprehension; a sense of foreboding; a transitory dyspnœa, even orthopnœa; substernal distress; palpitation; and some of the following signs: tachycardia, a slight increase in the respiratory rate, cyanosis, sweating, a fall in blood pressure, and other signs of moderate collapse. These signs and symptoms last 2 to 5 minutes. Patients who have experienced reactions of this type dread their injections because of such accompanying unpleasant sensations.[32]

Occasionally 1 to 2 hours after an injection, a typical asthmatic attack, or pulmonary œdema, has developed.[31]

Rarely, renal irritation with albuminuria has occurred following an injection.[8]

In almost all of the reported cases of sudden death following the use of a mercurial diuretic, there was a history of immediate non-fatal reactions with preceding injections, not always with same drug.[31]

Cutaneous eruptions, and chills and fever following an injection that are suggestive of an allergic reaction to mercury have also been described,[33] and a few of these were later followed by fatal reactions.[34]

Mercury poisoning, the result of the lack of excretion of mercury in the urine, has resulted in some cases in salivation, stomatitis, diarrhœa,[35] severe colitis, and rashes.[33] Salyrgan[35] is usually the offender.

Some non-fatal delayed reactions such as fever, erythema, and paræsthesia are specific for one drug, and are doubtless the result of the activity of the organic radical of the drug used.[31] Theophylline is not responsible for any of these reactions.[21]

Thiomerin causes almost no toxic reactions in experimental animals except in quantities far exceeding (160 times) the maximum tolerated dose of meralluride,[3] and none except mild local reactions have been reported in human beings.[29]

Reactions Related to the Associated Diuresis

A number of cases have been reported[32] in which 6 to 12 hours after injection, a "diuresis syndrome" follows, consisting of weakness, restlessness, mental confusion, apathy, and thirst not relieved by plain water; coma, and even death occasionally have resulted, and the rationale of these occurrences can be easily understood by a consideration of the results of diuresis by mercurials on the body acid-base balance.[36] In hot weather, the loss of sodium chloride and water in the perspiration may further aggrevate such a situation.[32]

Dehydration and hæmoconcentration have occurred in the presence of œdema, together with a negative chloride balance, as the result of mercurial diuresis; and oliguria, and even anuria, have followed in such cases.[37]

Mobilization of digitalis from the œdema fluid as the result of mercurial diuresis in fully digitalized patients has been claimed by Kissane and Koons[38] and other investigators to give symptoms of digitalis intoxication, in some cases several days after the last dose of digitalis.

Hyman[39] suggests that the toxic effects of the intravenous injection of a mercurial diuretic are not specific for it, but are the result obtained by rapidly injecting any material intravenously, par-

ticularly one consisting of large molecules. This over-simplified view is not widely accepted.

An examination of the reported cases of death following the use of mercurial diuretics shows that patients who are very ill, particularly those with a markedly diseased cardiac musculature,[32] are more apt to die from the results of mercurial intoxication than those in better health, but that good health is no protection against a fatal reaction.[31]

DOSE AND METHOD OF ADMINISTRATION

When giving a mercurial diuretic to a patient for the first time, 0.25 cc. should be injected intramuscularly, and, should fever, urticaria, or bronchiolar spasm result within an hour, it should not be used.[35]

The dose, intravenously or intramuscularly, is usually stated as 1 to 2 cc. of any of the liquid preparations listed above (0.5 - 2 cc. intramuscularly or subcutaneously for Thiomerin), but as Goldring has observed,[35] "the dose is variable, and should be defined as the least amount required to produce a significant increase in urine volume," which may be as low as 0.5 cc. .

According to New and Non-Official Remedies,[40] intramuscular administration, because of its equal efficiency and greater safety, is the method of choice. But the intravenous route, if used carefully, will eliminate the local reactions resulting from the intramuscular injection of mersalyl, mercurophylline, and, to a lesser extent, meralluride.[25] Thiomerin given intramuscularly obviates all of these objections.[29]

Either oral [41] [42], or rectal administration[43] [44], although resulting in much less diuresis than that produced by the intramuscular or intravenous method, is of value in the treatment of patients regularly requiring a diuretic of moderate potency, especially when used in conjunction with ammonium chloride. Toxic effects from either, when they occur, are minimal (e.g. gingivitis, gastro-intestinal disturbance), and disappear when the drug is discontinued.

When rapid diuresis is indicated, it has been recommended[45] that 6 Gm. of ammonium chloride be given daily for two successive days, before injecting a mercurial diurectic on the third day; this schedule may be repeated as required seventy-six hours later.

Should diuresis not result from the use of a mercurial diuretic, Goldring[35] recommends that no more than 3.5 cc. should be given over a period of 3 days (0.5 cc., 1 cc., 2 cc.), and that, after waiting one week, and then preparing the patient for 3 days with ammonium chloride (6 Gm. daily), should the administration of 2 cc. more of the diuretic still produce no diuresis, then the use of a mercurial diuretic in that patient should be discontinued.

Should mild delayed toxic reactions occur with one drug, very cautious administration of intramuscular doses (0.5 cc., then, after 1 day, 1 cc.) of another may be tried. If no untoward results occur, the use of the second drug may be continued if care is exercised.[31]

When a "diuresis syndrome" follows the use of a diuretic, water administered by mouth is more efficacious than water given parenterally. Sodium chloride in capsules, followed by 0.1 per cent solution orally, should also be given.[36]

Careful use of the mercurial diuretics involves: the use of a test dose; never repeating their use following any toxic reaction referable to the mercury ion; never giving them more than twice a week[46]; keeping the patient in proper

sodium chloride balance, especially when the environmental temperature is elevated; administering them intravenously very slowly, making certain that the needle is well within the vein throughout the injection,[46] ascertaining that the "vesical status" of middle aged and elderly men is adequate for the handling of an increased urine volume (residual urine of over 60 cc. is a contraindication)[47]; and restricting digitalis temporarily (according to some authorities[33]) before giving them to a fully digitalized patient.

SIDE EFFECTS

Following a marked diuresis, profound weakness with no other symptoms may result. Such an occurrence is not serious, and need not cause concern.[14]

USE: INDICATIONS AND CONTRAINDICATIONS

All writers on the subject stress that the mercurial diuretics should never be used without adequate positive indication for their administration, and then only with care.

In the treatment of cardiac œdema, the mercurial diuretics are of great value, but they should never be used unless the patient is unable to maintain an adequate cardiac output by rest and digitalis alone.[35] According to Goldring,[35] their usefulness in this regard is largely limited to cases with œdema resulting from chronic left ventricular failure, to those with extreme and incapacitating œdema or serious effusion, and to those with moderate œdema (for the psychic effect). Goldring[35] states that they are very important in the treatment of pulmonary œdema, and suggests a prophylactic weekly or bi-weekly injection in patients with a history of recurring attacks.

In New and Non-Official Remedies,[40] their use is recommended in cases of nephrotic œdema, and in carefully selected cases of the subacute and chronic forms of nephritis.

In the ascites of hepatic cirrhosis, their use cuts down[16c] (or eliminates, in one third of the cases[35]) the number of paracenteses necessary to keep the patient comfortable.

According to Goldring and Gold,[35] as long as the patient can excrete mercury, there is no danger accompanying the use of the mercurial diuretics. In New and Non-Official Remedies,[40] acute nephritis, and chronic renal disease with well-defined tubular and glomerular changes, are listed as contraindications; some include nephrosis.[48]

CONCLUSION

In his survey of the various therapeutic measures used in the treatment of congestive heart failure, Clark[46] states that "the mercurials are the most effective of the diuretics we have to-day," and he, with practically every other writer on the subject, recommends their careful use where clearly indicated. It is true that toxic reactions have occurred, but, as Ben Asher[32] and others have observed, the incidence of toxic reactions following their use is as low, if not lower, than that of other potent drugs used with equal frequency in the field of therapeutics.

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EDITORIALS

MEDICAL RESEARCH AT TORONTO

At the request of many of our readers we publish in this issue Part I of a fairly comprehensive outline of the major research projects that are being carried out at the University of Toronto. Written by G. Chertkow and M. L. A. Auerback, this article should make interesting and informative reading for both graduate and undergraduate.

By printing this article, the Editorial Staff of the JOURNAL hopes to pay tribute to all those gifted people who, by their investigative ability, enterprise and tenacity of purpose, are progressing toward new heights in the understanding, treatment, control and eradication of disease. These men and women, whom we keep anonymous lest we should embarrass them, are providing a living stream of knowledge rather than a stagnant pool from which the medical students of this school can drink.

EXCHANGE JOURNALS

Several undergraduate medical journals, published in other universities throughout the world, are received regularly through exchange agreements with us. Many of these publications recently have been put on display in the Medical Reading Room. Some of them contain predominantly serious articles, others provide the reader with humorous tales resembling, in some cases, those which resulted in the banning of "Epistaxis".

The Editorial Staff urges all undergraduates to examine carefully these journals. Those of you who over-enthusiastically proclaim the excellence of the UNIVERSITY OF TORONTO MEDICAL JOURNAL may find it a humbling experience; all of you should find it an interesting one.

FEATURE

MEDICAL RESEARCH AT THE UNIVERSITY OF TORONTO
PART I

G. CHERTKOW, B.A., 5T0
M. L. A. AUERBACK, 5T2

IT HAS BEEN SAID that the great advances made in Medicine during the past generation have had two significant results: the first, to lay the foundation for medical research into new fields, thereby stimulating the research workers to increased effort; the second, to excite an enthusiastic but often under-informed press to release wild stories of new and sensational discoveries and cures. We shall not take time to discuss this latter result; sufficient examples appear in the daily newspaper and weekly newsmagazine. Instead, we will endeavour to outline, briefly, some of the medical research currently being undertaken at the University of Toronto, for nearly all of it is an outgrowth of recent developments in medicine.

The work being done at this university cannot be classified as sensational. On the contrary, much of it is the difficult, unglamorous labour that lays the groundwork for the "miraculous" discoveries in which the newspapers love to revel. Probably one of the main reasons for the excellence of the research is that there is less of the autonomous insularity of individual departments that so frequently hampers research in other centres. The degree of interdepartmental integration is outstanding; there is a constant interchange of ideas, constructive criticism, and material aid. Further, the work is in the hands of men and women who are skilful enough to master their tasks, resourceful enough to carry on with such materials and funds as are available, and patient enough to work on the same experiment for years without any great assurance of final success.

DIABETES AND INSULIN

Ever since Banting and Best made their epic discovery of a method for isolating the pancreatic anti-diabetic hormone, *insulin,* for clinical use, many of the research facilities at this university have been devoted to the investigation of both the diabetic state, and insulin, with the aim of improving the lot of those suffering from this metabolic disease. So much work has been done during the past quarter century that today, Toronto stands as one of the foremost diabetic research centres in the world.

After it was recognized that diabetes may be associated with an insufficiency of insulin-secreting tissue, the *islets of Langerhans*, scientists began to search for ways to cause this tissue to grow, the hope being that if his lost hormone-producing cells could be replaced, the diabetic patient might be rendered independent of exogenous insulin, and indeed, cured. One of the big stumbling blocks to such investigation was the difficulty of ascertaining islet volume in experimental animals. Thanks to a new technique developed at Toronto, however, these volumes can now be determined relatively easily, with the result that investigations into the factors causing

the growth of this tissue are rapidly progressing. Already it has been shown that certain extracts of thyroid and pituitary have great effect in causing islet growth in rats. Unfortunately, however, in certain other adult animals these same extracts, presumably because of excessive stimulation of the islets, cause degeneration of the *beta*, insulin-forming, cells. The search still goes on; perhaps in our lifetime it will prove fruitful, and the diabetic will be restored to normal health.

An increasing amount of work is being done on insulin itself. At the moment, Toronto investigators are trying to find some way of assaying it in the blood. So far their results have been unproductive, but if their research proves successful a great stride will have been taken towards the understanding of the action of this hormone. Also being intensively studied are the effects that insulin exerts in the metabolism of carbohydrates. Results so far indicate a participation of insulin in reactions coupling the processes of phosphorylation and oxidation. It would appear that more efficient coupling occurs in the normal than in the diabetic organism.

While all this research goes on, the fact remains that the diabetic patient must continue to take his daily injections of insulin. To improve the commercial product, workers are constantly seeking for new and better methods of extracting and purifying insulin. Experiments seeking to reduce the number of injections that a diabetic must take are well under way. A difficult problem that must be overcome here, however, is the prevention of the dangerous hypoglycaemic states that might occur during periods of inactivity after large doses of insulin.

One of the big obstacles to work on diabetes is the length of time that must be devoted to the rather complex blood-sugar determinations. Recently, however, a new method was developed which may prove to be more sensitive and quicker to perform than the old methods. Many of the possible errors of the standard blood-sugar determination test are avoided because this is a colorimetric test not dependent upon reduction for the development of colour.

LIPOTROPHIC SUBSTANCES

During the past quarter century, certain substances profoundly affecting the transfer of fat in the body have claimed the attention of Toronto researchers. Several of these, insulin and anterior pituitary extract, are important for other reasons as well. The substances which have interested Toronto workers most of all have been the lipotropic agents, so named by Best. These are compounds which prevent the accumulation of fat in the liver, and facilitate the distribution of fat throughout the body. Of the four known lipotropic substances, choline, betaine, methionine, and inositol, choline has proved of greatest interest to experimenters.

It is now well established that an animal on a diet deficient in choline will develop a fatty liver, and later, cirrhosis. There is little likelihood that the average Canadian living on a normal adequate diet will ever develop cirrhosis. At the same time, the fact that chronic alcoholics frequently develop this disease, as do many poor, non-alcoholic groups in Asia and Africa, has led to fairly extensive experiments with rats in an attempt to discover the common factor. Rats fed alcohol and a diet deficient in choline developed fatty livers, while those given the same amount of alcohol with adequate amounts of choline added did not. To make the experiment even

more complete, sugar was substituted isocalorically for alcohol and the same results were obtained. (This, by the way, led to the rather amusing deduction of the press that soft drinks cause cirrhosis.) These experiments showed quite conclusively, under the particular dietary conditions chosen, that it was not the alcohol itself that caused the ill effects, but rather the disparity between the caloric and the choline intake.

Other investigators observed some ten years ago that the kidneys of very young rats on a choline deficient diet were nearly always enlarged and haemorrhagic. Now it had been well established that severe degrees of kidney damage produced by any of several methods is followed by the hypertensive state in experimental animals. These methods involved surgery or the injection of nephrotoxic materials. Would young rats that suffered kidney damage as the result of choline deficiency develop hypertension as they grew older? To provide the answer, a series of experiments were performed at Toronto in which periodic measurements of the blood pressure were recorded and correlated with the renal lesions which developed. It was found that a significant number of these rats developed high blood pressure. Thus, for the first time, hypertension in an experimental animal had been produced by a dietary deficiency alone.

Other lipokinetic factors besides the lipotropic ones are also being studied here. The importance of insulin in fat metabolism has been known for a long time. Now attention is being focussed on the effects of the anterior pituitary extracts. At the moment, several workers are studying the influence of these substances on the distribution and utilisation of fat in the body. It is hoped that these investigations will appreciably broaden our knowledge of the intermediary metabolism of fats within the next few years.

ANTIBIOTICS

Nothing has captured the imagination of the public so much as the discovery of the therapeutical uses of *penicillin*. Indeed, penicillin and the antibiotics that have followed it have become household words. Yet there are still vast fields for research, even with a well known drug like penicillin. At Toronto, work with the latter has centred about the finding of longer-acting forms that would obviate the necessity of repeated injections. At present, some workers are investigating the efficacy of certain penicillin-in-oil preparations, while others are evaluating ethyl and amyl tyrosine conjugates, developed at Toronto, which seem to be longer acting, possessed of local anaesthetic qualities, and less capable of producing hypersensitivity.

Recently, a striking discovery was made. It was found that a dog whose hepatic artery had been ligated would survive indefinitely if given repeated injections of penicillin for ten days following the operation. Why the penicillin should save the animal from practically certain death, and further, why it can be discontinued after ten days without ill effect to the animal are questions that workers are now attempting to answer.

Streptomycin, another great antibiotic, has become both famous and infamous. While it has proved to be very effective against many gram-negative bacilli, there is increasing evidence that bacteria, especially the tubercle bacillus, become very resistant to its action, and even so adapt to it that they require streptomycin for growth. Workers directed their attention to this problem of drug resistance, and began to experiment with mix-

tures of this antibiotic and other compounds. They found that when *para-amino salicylic acid* (*PAS*) was added to culture media, the tubercle bacillus did not become resistant to the streptomycin. This *in vitro* study has since been followed by collaborative studies at the Toronto Hospital for Tuberculosis, which showed that PAS combined with streptomycin in the treatment of tuberculosis delays the appearance of streptomycin-resistant strains in most patients treated, in contrast to the high incidence of resistance when streptomycin alone is used.

STUDIES IN METABOLISM

Although most of the research work so far described has been concerned with the alleviation of definite pathological conditions, one must not assume that investigators at this university neglect the study of the normal processes of life. At the moment, the metabolism of carbohydrates, proteins, and fats is the subject of a great deal of research, as are the effects on metabolism of certain environmental stresses. The actions and chemical makeup of certain enzyme systems important in metabolism are also being studied.

One of the big obstacles to the study of fat metabolism has been the difficulty in separating out the naturally-occurring glycerides, and phospholipids. It has long been felt that if these substances could be obtained in a highly purified state, the action of certain body enzyme systems upon them could be accurately observed, thereby increasing our knowledge of metabolism. To provide workers with these needed compounds, researchers at this university have developed methods of synthesizing pure substances of known configuration and constitution. Already they have produced synthetically a number of mono- and tri-glycerides, phosphatides, and related substances. They have also synthesized several compounds that are important in the intermediary metabolism of carbohydrates.

Several enzyme systems of great interest to Toronto workers are concerned with carbohydrate metabolism. They are the hexokinase and phosphorylase systems which are being investigated in an attempt to ascertain the factors regulating the flow of carbohydrates into the metabolic pool. Another set of enzymes that are being studied, this time in relation to myo-neural activity are true and pseudo cholinesterase.

A group of research workers are interested in the effects of certain stresses on normal activity. They are examining, in particular, the effects on the metabolism of rats kept at a low temperature. Results so far indicate that the rats eat more, but have decreased need for certain indispensable foodstuffs, especially choline. They are also investigating the effects of certain stress phenomena on endocrine activity with special reference to the effect of emergency situations on the function of the adrenal cortex. Within a few months this same group of workers will begin to observe the effects of a radioactive environment on living animals in one of the new radiation laboratories being built at this university.

CANCER

Scarcely a week goes by without the newspapers reporting a "discovery of the century" in the field of cancer research. While most of these findings are important and add to our knowledge about this disease, none as yet has proved to be the cure which the layman eagerly awaits. Although we cannot report the discovery of a "cure" by Toronto workers, we can

outline some of their methods of investigation and indicate, wherever possible, what has been accomplished.

Cancer has been defined as the "growth of new cells which proliferate without control and serve no useful function". Although a great deal is known about the process of growth, certain key facts still elude us. Scientists have long agreed that if we could discover these secrets, our task of defeating cancer would be made that much easier. It is for this reason that a group of researchers are now investigating the growth of normal cells. They have developed a chemically-defined completely synthetic medium, which supports the growth of normal tissues for some weeks. This, they hope, will enable them to determine cellular requirements and observe the effects on growth of altering the chemical nature of the growth medium.

The significance of viruses in carcinogenesis has been the subject of much study at this university. That viruses are probably important factors in maintaining the growth of tumours is shown by an experiment in which an active virus was recovered from a mouse mammary tumour that had been cultured in the yolk sacs of fertile eggs and transferred thirty times. Now the experimenters are attempting to culture the virus alone, without tumour cells.

At the same time, another group, employing isotopic carbon and phosphorous, is studying the relation of viruses to cells, especially with regard to the way in which a virus is nourished while it is within the cell.

The fact that tumours thrive upon transfer to fertile eggs has provided Toronto researchers with an efficient method of obtaining pure malignant tumours. They have found that by feeding a carcinogenic dye, butter-yellow, to rats, they can almost invariably produce a tumour of the liver. After several transfers through the fertile egg yolks, they can obtain a pure liver tumour which can then be subjected to the actions of certain chemotherapeutic drugs, or sectioned for various types of examination. One form of study is by the electron microscope to detect the different cytoplasmic inclusions in cancer cells. Another is by ordinary microscopy, to compare histologically, embryonic, hyperplastic, normal and malignant tissues. A third type of study is the examination of the particulates freed from the various types of cells, normal and malignant, by centrifugation.

Carcinogenesis and the treatment of cancer by radiation are the two chief problems with which another group of investigators have been concerned for several years. In regard to carcinogenesis, they have been carefully examining environment, or more particularly, the radiant energy of the environment that constantly flows through our bodies. To determine whether or not the removal of individuals from the influence of radiant energy reduces carcinogenesis, a thousand mice were placed half a mile underground in a mine, while an equal number were left at the surface as a control. It was found that half a mile below the surface, where even cosmic rays could not reach, there was still some radiant energy, much of which emanated from surrounding rock; furthermore, no significant decrease in carcinogenesis accompanied the reduction of radiant energy.

Radiation has long been used clinically to arrest the growth of, and to destroy, certain tumours. It has been found also that if a fowl is cured by irradiation of a Rous sarcoma, which is virus-caused, it is thereafter immune to this tumour,

and cannot be reinfected. This has directed researchers' attention to the influence of radiation in enabling tumours to induce an active immunity in the host following absorption. At present, they are working on the postulate that if tissue taken from an actively growing tumour in an animal is irradiated with rays of wave-length between that of ultra-violet light, and that of X-rays, with the object of causing a modification of the molecule, while the original tumour is killed by other lethal radiation, the transplant, on being restored to the tissues of the same animal, may be modified to give a lasting immunity to the animal. If it could be positively established that irradiation with certain wavelengths changed the tumour-causing virus so that it was no longer carcinogenic but could still induce a state of immunity in the host to a particular type of tumour, a great stride would have been made in the fight against cancer. The fact that we cannot substantially reduce the possible carcinogenic features of our environment suggests that the immunological approach may be a significant method of combatting cancer.

CONCLUSION

This has been a brief examination of some of the medical research being carried on in certain departments of the University of Toronto. Grateful acknowledgement is made of the kindness shown by the members of the staff of the Faculty of Medicine, and its related research centres in giving us all the material we required and offering constructive criticism of this article.

Next month we shall continue this study of medical research at the University of Toronto.

HUMANISM AND MEDICINE

H. B. VAN WYCK[1]

PART XI

THE REVIVAL OF LEARNING AND THE RENAISSANCE

The 14th and 15th centuries are usually considered the centuries of the Renaissance, but from the 12th century European man may date the revival of learning and the reawakening of the intellect. The centres of recovery were for the most part the universities and the religious foundations. The Order of the Dominicans or Black Friars was founded at Toulouse in 1215 by the austere and orthodox Dominic. The name of Dominic is associated with the persection of the heretic sect, the Albigenses, and the Dominicans, impelled by a fierce orthodoxy, set themselves to the task of defending Church doctrine and extirpating error. This preoccupation with orthodoxy was allied to the activities of the Inquisition and the Dominicans, whose title was paraphrased as the "Hounds of the Lord," *Domini Canes*, have retained an unamiable tradition with Torquemada as a central figure. On the other hand, the annals of the Order are adorned by the great intellectual achievements of Albertus Magnus (1206-1280), and St. Thomas Aquinas (1227-1274).

The Franciscans or Grey Friars on the other hand, were founded in 1209 by the gentle and loving Francis of Assissi, and his radiant figure typifies what was best in mediæval piety. The greatest saint of the Middle Ages was both a mystic and an ascetic. A mystic is one who derives truth directly by revelation. Mysticism, by directing the soul to unmediated communion with higher powers, favours toleration of religious differences, hence the all-embracing charity in the legend of St. Francis. He was also an ascetic in the true sense of the derivation of the word from the Greek, "ascesis", which means a training by the discipline of self-denial, a training for a race or contest. Most religions have developed ascetics—those who retire from the world and live in self-abnegation. Sometimes this has been merely a flight from reality to the safety of a cloister and the protection of superstition. In its nobler forms asceticism has been actuated by a desire to practise virtue free from the temptations of a gross world, or to enjoy the contemplative life of a visionary. When these pure motives have been reunited to an urge to the service of humanity we see asceticism in its noblest guise. Of such was St. Francis. Such figures adorn their age and are remembered by man with the poets when the soldiers, the despots, and even the philosophersmay be forgotten. When such examples of moral elevation appear, a contemporary and cynical generation, however, may put them to death. By such Socrates was given poison, Christ was crucified, Joanne of Arc was burned at the stake, and a Lincoln or a Gandhi are shot.

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That St. Francis lived to a ripe old age is a measure of the value that the European peoples of the Middle Ages put on character and moral purpose. Because of this it is fitting that before discussing the philosophic and scientific revival which began with the 12th century the main features of this saintly life may be outlined. Ignorant of science and the higher flights of the intellect, the common people of his time, whom we regard as unenlightened, found in the simple conduct of this humble friar a thing of beauty and a stimulus to the good life, for he really practised the impracticable ethics of Christianity. Whenever character becomes prized above intellect, man's sense of values has been restored to health and sanity. This precious element in the Middle Ages, this pre-eminence given to moral values tended to be lost in the feverish intellectual new birth of the European intellect; but however obscured man's vision may ever become by scientific and technical so-called progress, the life of St. Francis, with that of his great prototype, will continue to prick the conscience of posterity.

Founder of the Franciscans, he was born in 1181. The beauty and strength of his character stand revealed in innumerable anecdotes. To quote Butler, "Probably no one has ever set himself so seriously to imitate the life of Christ." He combined a sincere desire for self-denial, poverty, and service to his fellows with a joyous love of nature. It would be an anachronism to think of St. Francis as a philanthropist, a social worker or a revivalist preacher. He fulfilled the functions of all three but was beyond all this an ascetic and a mystic with a great and forceful personality. The Order he founded has had a stormy history, but Franciscans of every age have faithfully carried on the saint's great work of ministering to the poor.

The legends that tell of the life of St. Francis have given many themes of great beauty to poetry and pictorial art. His love of animals, a dominant passion, was perhaps the first conscious introduction into our modern way of thought of a humane consideration for animal life. It has been remarked that such seems completely absent from either the Old or New Testament. The naïve legends of St. Francis preaching to the beasts of the field is a symbol of the humaneness that must have at times characterized mediæval man when not blinded by fear or fanaticism. The modern counterpart of this extension of humanity to the lower animals has produced the Humane Society—a paradox in a war-torn world. The tradition of St. Francis will always remain a precious memory of a simple, lovable, mediæval saint.

The first impulse to revival of learning was the recovery of the writings of Aristotle and their interpretation by Albert and St. Thomas, who attempted a synthesis of reason and philosophy to parallel the accepted structure of ecclesiastical doctrine. There was, however, very little evidence of the rise of a faith in the reality and value of scientific knowledge, for there was very little evidence of any effort to learn by direct observation of nature. The mediæval mind was obsessed with the idea of a mortal finite world, both fully knowable and not worth knowing. St. Augustine wrote:

"Men seek out the hidden powers of nature, which to know profits not. Even if the causes of the movements of bodies were known to us, none would be important except such as influence our health. But since being ignorant of these we seek physicians, is it not clear that we should

rest content to be ignorant of the mysteries of the heavens and the earth?" (De Fide, 16).

It need not surprise us that medicine had deteriorated into conventional lists of drugs, and that the infinite realms of science in general which modern man explores were not dreamed of by the intellectuals or the scholastic philosophers, as St. Thomas Aquinas and his contemporaries were called. The task of the scholastics was to formulate a picture of the universe in accord with spiritual truth rather than to search for new truths, and scholasticism was an effort to combine the loyalty of the intelligence with that of the heart, to reconcile faith and reason. For this they naturally relied largely upon deduction, which they handled with extraordinary skill and whether one admits that this aim has been achieved, no one may deny the impressive intellectual monument which the scholastic philosophers created. Among these the dominant figure was St. Thomas Aquinas (1225-1274). Educated in the Monastery of Monte Cassino, St. Thomas lived to be the greatest intellect of his age. No theologian, with the possible exception of St. Augustine, has had an equal influence in the theological thought of the western Church, or indeed, on the scientific thought of his day. He was called the Doctor Angelicus, and his importance in the history of modern Europe is that he produced the astounding synthesis of past philosophical thought known as Scholasticism. Scholasticism was an attempt to reconcile the body of Christian doctrine with the scientific and philosophic tradition. It accepted the teaching of the Church and found the interpretation of science to conform to that teaching. Thus it made Aristotle infallible and raised Galen to the height of a divine oracle. To-day in Russia there is a tendency to make art and science conform to the ideology of Communism. These must conform to the dogma, say the disciples of Karl Marx, that the primary motive in the history of mankind is the economic motive, the search for food. Many modern thinkers regard this as a modern equivalent of Scholasticism. The deductive approach to experimental data is, however, limited, and science must progress not by the over-exploitation of deduction which tends to be a reversion to Scholasticism, but by empiricism and induction.

It is not right, however, to assume that the strong antagonism felt by many scientists to scholastic tendencies is necessarily antagonism to religion, for the domains of science and religion are essentially different. Science is reason applied to the experimentally obtained data of the world of the senses, whereas religion is often a rational abdication of reason in a sphere not amenable to the methods of science. Conflict arises only when the spheres of each become confused.

However, although few of the mediæval writers were real observers of nature, there are evidences, for example in the works of the great Albertus, that the scientific spirit was beginning to awaken to a new dawn. Among the contemporaries of St. Thomas were several Franciscan writers who may be termed the first consciously scientific thinkers since antiquity. Such were Robert Grosseteste (1175-1253), Bishop of Lincoln, who appears to have actually experimented with lenses; the mathematician, John of Peckham (1220-1292), Archbishop of Canterbury; and the greatest figure in mediæval scientific zhought, Roger Bacon (1214-1294). Born in Somerset into a prosperous family, Bacon

went up to Oxford where he took Orders in 1233. From Oxford, he went to Paris and there won the degree of Doctor of Theology. In 1250 he returned as lecturer to Oxford where this strange monk dealt not with religious subjects but with science and education. The essentially sceptical and inquiring nature of his mind, which refused to accept traditional learning solely because of ancient authority, branded him from the beginning as heretical. Ordered by the Franciscan General Bonaventura, Bacon returned to Paris where he was held virtually a prisoner for ten years, deprived of all materials for study and shut off from all contact with cultivated men. In 1265, Pope Clement IV ordered Bacon to write a virtual encyclopædia of all science. The *Opus Majus*, one of the three treatises, gave forth a new voice to the becoming modern world, the first clear call to scientific research since Archimedes. This book reverberated like the explosion of a bomb. Here was a deeply religious man, perspicuously honest, who stated that certain truths could not be discovered by closing the eyes but by opening them to experiment. Bacon wrote much of the principles of light and the effects of lenses. He experimented with mechanical devices in which it would appear was germinating the mechanical triumphs of the coming centuries—the steam engine and the aeroplane. All this was black magic to the most of his contemporaries, and when his patron at the Vatican was followed by Nicholas III, who lacked the liberalism of his predecessor, Bacon was again thrown into prison. Fourteen years after, broken in health, he was released, two years before his death. As the greatest thinker of his time looked back on his frustrated life, he wrote:

"It is on account of the ignorance of those with whom I have had to deal that I have not been able to accomplish more."

The transmission of Greek science from the Arabic world had been for centuries a powerful influence on mediæval culture. As early as the 9th century, a stable and united Moslem empire with its centre at Baghdad, stretched from Persia to Spain, and the Moslems developed an increasing interest in the learning of the Graeco-Roman world. One by one the medical and scientific writings which the Greeks had left were translated into Arabic and, in this alien tongue, the science of Hippocrates and Aristotle and the philosophy of Plato and Plotinus were spread far and wide. The Arabic-speaking students of the Mohammedan universities began to have a better knowledge of Greek science than their contemporaries in Christendom, at least until the 12th century. A certain number of Arabic authors produced original works not without some value. Rhazes (860-932) of Basra wrote a work containing the first known description of measles. Another Persian—Avicenna (980-1036)—composed the *Canon*, a vast encyclopædia of medical knowledge which served as a textbook of medicine in both the Moslem world and the Latin West until as late a period as the 17th century. A Spanish Moor—Albucasis (1150)—left a textbook of surgery which stimulated the revival of the subject in Italy and France. To obtain these scientific treasures and translate them into Latin, many adventurous spirits travelled from Christian Europe to Spain and Sicily where, assisted by native Jews and Mohammedans, they brought back precious cargoes of learning to the universities of Christendom. This exotic influence reached its zenith by the 12th century and contributed much to the

renewal of interest in science and philosophy which subsequently flowered in the 14th and 15th centuries during the Renaissance. It must be noted, however, that the literature of ancient Greece reaching the western world through translation successively into Syriac, Arabic and Latin suffered much from inexact reproduction, annotation, and deliberate alteration, and the original matter often became buried under so much comment, refutation, and argument that the essential pristine state of classical literature was not recovered until the inquiring spirit of the Renaissance took men back to the pure and original sources. The rediscovery of the pure texts and unalloyed ideas of the Greek and Latin poets, philosophers and scientists marked a revolutionary change in the learning of our western world. The revival of interest in this old literature was carried out by the scholars of the universities of Christendom, aided by the influx into Europe of many cultured Greeks after the fall of Constantinople before the Turkish hordes in 1453. These rediscoverers of ancient treasure were called the Humanists, and their interest-Humanism. This restricted use of the word meant that these newer studies were the secular "humanities" as opposed to the disproportionate interest in theology, "the divinities", which had dominated the universities until this time. The word "humanism", however, has been greatly enlarged in meaning since this era and may now be taken to include all the interests that centre around the personality of man, the arts, philosophy, and religion itself. By this definition, humanism is sharply defined from mathematics and the natural sciences.

And now about the 14th century the reawakening of European man's interest in science coincided with the work of the humanistic revival. Each movement reciprocally aided the advance of the other and produced the flowering of western man's intellectual progress called the Renaissance. To this great cultural advance, incalculable aid was given by the discovery of printing by Coster and Gutenberg in the middle of the 15th century. For the first time, accurate compendia of classical learning and science were available and it was now possible for these to be widely distributed and not merely the possession of a few monastic clerics. The coincidences of these influences made an astounding and abrupt change in European culture and produced our modern world.

To give the barest outline of the changes which marked the transition from the mediæval world, many a volume would be required. The advance in science and humanism to be understood must be depicted against a rapidly shifting economic and political background. With the decay of the feudal system and a rural peasantry came the growth of towns, increasing trade from beyond the confines of the Latin world, and the rise of an urban middle class; and, parallel to the decline of the unifying concept of a homogeneous Christendom appeared the rise of nationalism with the crystallization into the rival states of modern Europe and the disintegration of one Church into numerous warring sects. This new birth of modern Europe took place at a time when adventurous globetrotters discovered new continents and old static civilizations. In the span of a few generations man took his longest step forward towards a brave, new world. It was progress, although perhaps not in every respect in the right direction. New

modes of thought and new facts tend to destroy as well as create; and change, although inevitable, as modern man has found to his dismay, is not necessarily always on the highway to the Elysian fields. In the centuries of the Renaissance began a vigorous and fruitful growth of the natural sciences and the fine arts. Life tended to become much more comfortable and safe. The conquest of the forces of nature has steadily spread, but it is obvious that modern man in his knowledge of himself and his perception of moral and æsthetic values has not kept pace with his greater mastery of physics and chemistry. The stimulus, however, to the advancement of medicine was first to be noted in the remarkable achievements of the anatomist, the physiologist, and the biologist, and their contemporaries, working in physics and chemistry. That these achievements did not produce a corresponding amelioration in the lot of the victims of pain and disease until the comparatively recent beginning of our present century is a phenomenon seeking explanation. Indeed, although rapid and continuous progress since the Renaissance was made in the ancillary biological sciences upon which medicine depends, the lot of the sick and wretched remained unalleviated until the era beginning with Pasteur. Modern science produced the Industrial Revolution before it reached the bedside.

Before outlining the stages of the scientific revival one may comment on the changed point of view in matters religious, social, political and economic. There are, however, many vestiges of the older world in the mode of thought of the great masses of people in the western world. Those who dwell in the country are more conservative than the populations that have been aggregated by modern industry, and among the former there still persists a belief in charms, necromancy, in astrology and in pseudo-scientific data that the modern rationalist has been impelled to discard. Some of these venerable prejudices remain fossilized in the culture of European peasantry and others may be seen in the formal ritual of ecclesiastical rites. The confusion between the fields of religious faith and scientific data still persists in the half-enlightened products of modern mass education. The age of reason has been unable to define the limitations of reason and interpretations of religious and æsthezic values are still involved in obscurantism and at variance with the hard, stubborn facts of a practical world. The social condition of those who till the soil in the more backward provinces of the old Austrian Empire or the Balkans has been late in experiencing any marked improvement, and, although our modern cities have been cleansed at last of pestilence, industrial slavery is a poor exchange for the organization of the crafts and guilds of mediæval Europe. To-day, with the political retrogression towards despotism as the only solution to class warfare and anarchy, the Utopia that seemed so near to the author of the *Novum Organum* recedes beyond the visible horizon.

Nevertheless, in the new Europe, and in the Americas as a consequence, there is a clear, broad contrast between the mediæval and the modern. No longer is science the monopoly of a sacerdotal church; a society divided between lay and cleric has given place to a society divided into rich and poor; and, while mediævalism was hostile to free inquiry, the modern atmosphere is congenial to the maturation of science. At the Renaissance, the lay mind stimulated by the free use of the vernacular

languages, fortified by more accurate knowledge of the classical tongues including Hebrew, was ready to plan its own progress. The book of nature was opened and modern science had begun. The human body became the predominant interest to the painter, and its dissection became the supreme task of the anatomist. The Copernican discovery that the earth revolved around the sun displaced the older geocentric cosmologies. Europe turned its attention from the commentaries of the old libraries in which the Scholiasts had written in "letters of opium on tablets of lead." Discovery, printing, invention, scholarship burned with a new flame in man's consciousness and Europe thrilled to Bacon's challenge that

"Truth is the daughter not of authority but of time."

Trade which had quickened during the Crusades now received fresh stimulus because of the importation of silver from the Americas. Great houses of opulent merchants and bankers rivalled the feudal nobles in financial and political power. Into this new-born world become inflammable with new knowledge and enlarged boundaries, and unstable from national rivalry and commercial greed, came the revolution, inevitably following soon upon the Renaissance, known as the Protestant Reformation; and this was followed by the counter-Reformation and decades of savage religious war. Of this aspect of the change in intellectual climate it is obvious to the unprejudiced that while much was gained, much was lost. Just as in the economic realm freedom and security seem antithetical, so it may not be wide of the mark to find a similar analogy in the religious realm. How to preserve one without losing the other is a present problem; and the historian, H. A. L. Fisher, closes his chapter on the New Europe with the following paragraph:

"A Chinaman of the period, had he been in a position to survey the turbulent European scene during the 16th and 17th centuries, might well have asked himself whether the art of living was not better understood by a people which had no religious quarrels because they had no religion but only an ethical code of deportment, whether the vast liberation of human forces brought about by the Protestant Reformation with all its infinite consequences for art and music, science and letters, was worth the price of long and savage wars, and whether an attitude of mind towards the ultimate mysteries less aspiring, less heroic and less confident than that which prevailed among Western Christians was not in effect more conducive to human comfort."

To turn from this cynical summary of the post-Renaissance centuries and to consider the concrete advances in science and medicine will be a welcome change.

ABSTRACTS

MEDICINE

The Rosacea Complex, Including its Ocular Component, E. P. Cawley and A. C. Curtis, American Practitioner, **4**: 119-123 (Nov., 1949).

The author has reviewed the clinical features, complications, ætiology, pathology and treatment of rosacea and given an analysis of 350 case records.

Rosacea is a facial disorder characterized early by transient episodes of erythema and vasodilatation and later by papules, pustules and enlarged glandular orifices and with minimal subjective manifestations.

Some longstanding cases develop rhinophyma—an increase in size of the nose in regular fashion or as irregular lobulated masses, dark red or dusky purple in color. Occasionally rhinophyma occurs alone.

Ocular rosacea is common and may consist of blepharitis and/or conjunctivitis or keratitis with possible corneal opacity.

The chief age incidence of rosacea is 35 to 50. It frequently coexists with seborrhœic dermatitis or the seborrhœic state. Gastro-intestinal disturbances are more common than in other dermatoses. Aetiological factors still considered include the seborrhœic habitus, nervous factors, gastro-intestinal disturbances, intake of caffeine and hot beverages, focal infection, avitaminosis or dysvitaminosis (B complex) and endocrine dysbalance. Differential diagnosis includes seborrhœic dermatitis and rosacea-like tuberculid.

Definite improvement is seen in most cases treated with simple topical measures, superficial X-ray, large doses of crude vitamin B complex orally and relief of gastro-intestinal disturbances. Rhinophyma is best treated by removing redundant tissue with the electrical cutting current. Treatment of ocular rosacea is best carried out in co-operation with an ophthalmologist who may utilize warm compresses, antiseptic eye drops, powdered calomel, beta radiation, surgical intervention or cauterization for corneal ulcers.

W. J. D. Cooke

Approach to the Diagnosis of the Common Types of Congenital Heart Disease, D. I. Rutledge, Journal of the American Medical Association, **141**: 1290-1297 (Dec., 1949).

Most important congenital defects can be correctly diagnosed by the physician who has a knowledge of certain basic facts and who inquires into history, uses his hands and stethoscope and in certain instances makes use of electrocardiograph and fluoroscope.

One hundred cases were studied at the Lahey Clinic and 92% of these fell into four common groups of congenital heart disease. Septal defects both auricular and ventricular formed 48%. Auricular septal defect (30%) may be considered when a moderately loud and harsh systolic murmur is heard along the left sternal border in the 2nd and 3rd interspaces in a non-cyanotic, poorly nourished and poorly developed patient, with right axis deviation and a prominent, pulsating pulmonary artery and a large right ventricle. Management of this defect is medical. Ventricular septal defects (11%) present a loud, harsh, systolic murmur heard best along the left sternal border, widely transmitted and usually accompanied by a thrill, with little or no change in size or shape of heart. Coarctation of the aorta (20%) should be suspected whenever a difference is encountered in blood pressure levels of the upper and lower extremities, with pulsations of the abdominal aorta and femoral arteries diminished or absent and a rough systolic murmur heard as well in the back as along the left sternal border. Diagnosis is confirmed by notching of the under surface of ribs in X-ray. Treatment is surgical. Patent ductus arteriosus (12%) should be considered if the patient has a loud, continuous, humming murmur heard best at the pulmonic area, low diastolic blood pressure, and fluoroscopy reveals an enlarged pulsating pulmonary artery with an enlarged, left ventricle. Treatment is surgical. Tetralogy of Fallot (12%) should be considered in a cyanotic child who has a rough systolic murmur and right axis deviation in the E.C.G. and who on fluoroscopic examination has an enlarged right ventricle with a small pulmonary artery. Treatment is surgical.

The real service given to the patient by the physician who recognizes a condition amenable to surgical treatment is emphasized.

H. R. Rowsell

OBSTETRICS AND GYNAECOLOGY

Peritoneal Pseudomyxoma: A Study of Four Unusual Cases, E. D. Rosenfeld, Arch. Path., **48**: 255-273 (Sept., 1949).

Four cases of peritoneal pseudomyxoma are reported, each with features of special interest. Two cases showed hypoglycæmia which the author believes is due to a combination of faulty absorption, hepatic insufficiency, and debilitation due to mechanical interference with the functions of the bowel and the liver.

The difficulties of diagnosis and the problem of distinguishing peritoneal pseudomyxoma from mucogenic adenocarcinoma are discussed. The author suggests that in females, peritoneal pseudomyxoma may originate in the appendix even in the presence of an ovarian cystadenoma, and strongly advises that the appendix be removed in all cases in which doubt exists in regard to the differential diagnosis.

D. A. Smith

Pregnancy Associated with Hypertension and Intracranial Hemorrhage, M. S. Goodfriend, M. D. Kein and S. M. Smolev, American Journal of Obstetrics and Gynecology, **58**: 770-776 (Oct., 1949).

The authors consider 5 cases of pregnancy complicated by intracranial haemorrhage which have occurred in their hospital over the last 20 years. The frequency of such a complication is only 1 in 5000, but since 4 out of their 5 patients died, they feel the cases require careful analysis.

All of the patients had a pre-existing hypertension, 3 had essential hypertension, 1 had chronic nephritis and the other had cardiovascular disease.

Two of the patients had a late toxæmia superimposed on the hypertension but the authors point out that in women with pre-existing hypertension and coexisting toxæmia, the presence of cerebrovascular haemorrhage passes unrecognized because the presence of headaches, drowsiness, hypertension and increasing albuminuria are attributed to the former conditions.

Since all the cerebrovascular accidents occurred after $7\frac{1}{2}$ months of pregnancy, it seems likely that the increased blood volume and circulatory load played a part.

The authors conclude that in women with a past history of rupture of an intracranial blood vessel, future pregnancies should be avoided, or if haemorrhage is noted early in pregnancy, therapeutic abortion is advocated as soon as the patient's condition permits.

N. Kerbel

SURGERY

The Surgical Treatment of Peptic Ulcer, W. P. Kleitsch, American Journal of Digestive Diseases, **16**: 428-430 (Dec., 1949).

Most patients with peptic ulcer are best treated medically. Absolute indications for surgery are:

1. Stenosis and obstruction.
2. Severe hæmorrhage. A single severe hæmorrhage in a patient over 40 and two severe hæmorrhages in a patient under 40 are taken to be indications.
3. Perforation. This is a surgical emergency. The author feels that there is no place for conservative treatment in any of these cases.
4. Intractable pain. This usually means penetration into the head of the pancreas or other viscus.
5. Gastric ulcer in a patient over 40. If the patient is under 40, an adequate medical treatment is employed for a short time. Unless healing is complete, surgery is undertaken.

Possible indications for surgery are:

1. Inability to follow medical régime. If hours of work and nature of employment make following of therapeutic program impossible, or the patient is of low intelligence, surgery may be indicated.
2. If ulcer discovered during operation for another abdominal condition, such as biliary tract surgery, it may on occasion be advisable to treat the ulcer.
3. Chronicity. This implies failure to be relieved by an adequate medical régime.

The operative procedures are:

1. Subtotal Gastrectomy—usually the procedure of choice. Occasionally vagotomy is also done if the patient has a "gastric personality."
2. Gastrojejunostomy. This is rarely used except in inoperable carcinoma or in older people with achlorhydria. Gastrojejunostomy plus vagotomy is occasionally used in poor risk patients.
3. Vagotomy alone is rarely used because of postoperative gastric stasis. Transthoracic vagotomy is indicated for stomal ulcer.

The number of failures is less than 1%, while the operative mortality is less than 5%. In the author's series, mortality was much lower in

patients under 50 than in those over 50. Complications such as postoperative diarrhœa and failure to gain weight were infrequent.

S. H. WITZEL

Etiology of Primary Varicose Veins, Histologic Study of One Hundred Saphenofemoral Junctions, F. B. Wagner, Jr., and P. A. Herbert, American Journal of Surgery, **78**: 876-880 (Dec., 1949).

Varicose veins have been attributed to two main causes:

1. A mechanical or hæmodynamic factor.
2. Inherent structural weakness of the veins themselves.

Choosing the saphenofemoral junction because of its constancy in anatomical structure, presence of a valve and because it is a perforating vein at a common site of retrograde flow in varicose states, the authors examined 100 removed at autopsy. In only 8 specimens could the diagnosis of varicose veins be made at autopsy. The saphenofemoral junction was exposed in situ and removed in toto and prepared for histologic study. The authors found that absence of smooth muscle and internal elastic membrane in the sinus wall of the valve area was fairly common. This defect may be congenital and possibly hereditary.

It is possible that such defects in other perforator veins would predispose to dilatation under constant back pressure rendering the valves incompetent and permitting retrograde flow of blood from the deep into the superficial veins.

A. BERNSTEIN

THERAPEUTICS

The Use of Urecholine in the Prevention of Postoperative Distension, C. E. Stafford, A. I. Kugel and A. Dederer, Surgery Gynecology and Obstetrics, **89**: 570-572 (Nov., 1949).

Urecholine, one of the choline derivatives, has been used to stimulate gastric motility following vagus resection for peptic ulcer. It is not destroyed by cholinesterase and has not the nicotinic action of doryl. When administered in therapeutic dosage sublingually, orally, or subcutaneously, it has little or no effect on the heart rate, blood pressure or peripheral circulation of normal human subjects. It does increase peristalsis and stimulates micturition and defæcation. When given intramuscularly or intravenously, it does not act selectively on the gastro-intestinal tract and can produce a fall in blood pressure with circulatory collapse. These effects can be abolished by the intravenous use of atropine.

This drug was given a clinical trial. One hundred patients who had had major surgical procedures done were given 10 mg. of urecholine sublingually three times daily beginning the day following surgery. Another one hundred similar patients were observed as controls. Further observations were made on patients who were given 5 mg. of urecholine subcutaneously for severe gaseous distension.

In the control group, 28% of the patients showed no evidence of abdominal distension while in the urecholine treated group 45% were free from abdominal distension. There were no undesirable side effects in the patients treated with urecholine sublingually.

In those patients receiving the drug subcutaneously, flatus and stool were passed as soon as 5 minutes after administration. A few complained of sweating, nausea and abdominal cramps which usually subsided within 15 or 20 minutes. Sweating was the most frequent of the effects noted. The drug is contraindicated in bronchial asthma, peritonitis and acute inflammations of the gastro-intestinal tract.

M. FIER

NEWS AND NOTES

Medical Society

On February 15, at the Royal York Hotel, the Medical Society sponsored a very successful Meds At-Home. Patrons and patronesses included President and Mrs. S. E. Smith, Dean and Mrs. J. A. MacFarlane, Dr. and Mrs. H. Wasteneys, Mr. R. F. Hetherington, and Miss D. M. Stillwell. The Dance Committee, headed by Gord Cameron, deserves a great deal of credit for providing the Faculty with a dance of such high calibre. The entertainment and the decorations were particularly outstanding. Proceeds from the corsages, which were sold at the door, went to I.S.S.

* * *

On January 25, in the Banting lecture theatre, Ettore Mazzoleni, Principal, Royal Conservatory of Music, spoke to an enthusiastic Medical Arts and Letters Club audience. His topic, "49 or 50?" dealt with the state of music in the twentieth century. February 8, in the Wycliffe Auditorium, the Arts and Letters Club presented the Oakwood High School Choir in a programme of fine music.

* * *

Two Faculty musicians who have been heard in concert recently are Dr. R. K. Graham, Demonstrator in Anatomy, and Mr. E. F. W. Baker, Meds 5T1. Dr. Graham presented a Hart House Sunday Evening Concert, and was also heard playing the Sibelius Violin Concerto with Sir Ernest MacMillan and the Toronto Symphony Orchestra. Mr. Baker was heard in a Tuesday noon recital at Hart House.

* * *

On February 2, members of the Medical Women's Undergraduate Association presented a musical evening at the School of Nursing. Dr. Florence McConney addressed the meeting which followed.

* * *

Work is progressing favourably on "Reflex", the first edition of the Medical Year Book. Pictures have now been taken of all the Faculty undergraduates. If you have not yet placed your order for "Reflex", you are urged to contact some member of the Medical Society Executive and do so at once.

Recent undergraduate scholarship winners include Mr. C. D. Anderson, Meds 5T5, who has been awarded a Medical Alumni Association Scholarship, and Mr. J. W. B. Redford, Meds 5T3, who has been awarded a Jay J. Allen Award.

* * *

Fraser "Moose" Mustard, Meds 5T3, has been voted by his team mates winner of the Johnny Copp Memorial Trophy. This trophy is given every year to the member of the Senior Varsity football team who is judged the most valuable player by the members of the team. The trophy is in memory of John Copp, Senior Varsity football player, who died in 1933 while in his fourth medical year. It is awarded on the basis of strength of character, as well as playing ability. Mustard has starred in the middle-wing spot on the Varsity Blues for three years, and has been hailed by coaches as one of the best line-men in Canadian football.

* * *

Nominations for next year's Medical Society Executive will be open from February 17 to February 24. The elections will be held the following week, the date to be announced. The Medical Athletic Association hopes again this year to hold its annual Spring Athletic Dance the night of the elections.

Camsi

Camsi movies are being shown in Room 138, Medical Building, every second Tuesday afternoon.

* * *

The Toronto Camsi executive announces that every effort is being made to assure publication of the Camsi Summer Employment Placement Service lists as soon as possible.

Faculty

Dr. W. L. Robinson, Professor of Pathology, and Associate Director of Applied Pathology, has announced his retirement from the University teaching staff at the end of this school year.

* * *

A recent visitor to the University Medical School was Dr. Bhatia, Dean of the Faculty, and Professor of Medicine, University of Lucknow, India.

On January 25, Phi Delta Epsilon Fraternity sponsored a lecture by Dr. Sidney Alexander Portis, Associate Professor of Medicine, Rush Medical College, Chicago, Illinois. Dr. Portis discussed "Newer Concepts in the Aetiology and Treatment of Idiopathic Ulcerative Colitis".

* * *

Professor F. G. Young, of the School of Biochemistry, University of Cambridge, delivered the Banting Memorial Lecture on February 13.

* * *

Sir Reginald Watson-Jones will be visiting Professor in the Department of Surgery, University of Toronto, February 21 to 28.

* * *

A federal government grant of $7500 has been given to the Connaught Laboratory of the University of Toronto to aid in the development of the production of ACTH. Small quantities have been made in Toronto already, but it will be some time before full-scale production can be begun.

* * *

Announcement has been made recently of three grants to aid poliomyelitis research at the University. A $28,990 March of Dimes grant, from the National Foundation for Infantile Paralysis, will enable scientists at the Dufferin Division of the Connaught Medical Research Laboratories to attempt to develop a high strength poliomyelitis anti-serum for possible protection against the disease. The work is to be done under the direction of Dr. C. E. Van Rooyen, Professor of Virus Infections, and Dr. A. J. Rhodes, Associate Professor of Virus Infections. A further grant of $5150 from the National Foundation for Infantile Paralysis will aid Dr. D. Y. Solandt, Professor of Physiology, and his workers to complete their basic studies aimed at eventually improving physical therapy techniques for the treatment of the disease. The estate of Misses Jessie and Christina Niven recently left $9000 to the University for research in poliomyelitis.

* * *

Other recent gifts include $300 from Mrs. Elizabeth Chudleigh to aid University research in heart disease, and a further $500 donation from Mr. and Mrs. G. Roy Sproat to maintain the G. Roy Sproat and Katherine Sproat Bursary Fund for ex-service students.

Dr. William A. Goldie, member of the Faculty of Medicine teaching staff from 1898 to 1929, died recently at his home in Toronto. Dr. Goldie worked with the University Pathology and Bacteriology Departments for some time, and later joined the Department of Medicine where he was on the staff of the Toronto General Hospital and the Hospital for Sick Children.

ALUMNI

Representatives of the Medical Alumni Association on the Board of Directors of the University of Toronto Alumni Association include Dr. T. G. Heaton, Dr. W. A. McTavish, and Dr. J. L. King.

* * *

The Medical Alumni Association has recently agreed to co-operate in the University of Toronto Alumni Association plan to establish composite branches of alumni in the smaller centres throughout the Dominion.

* * *

Early in March, a panel on General Practice, for final year undergraduates and internes, will be held at the Toronto General Hospital.

* * *

Dr. W. J. Deadman, Pathologist, Hamilton General Hospital, has been named "Man of the Year" in Hamilton.

* * *

The Medical Alumni Association has announced that, in the academic year 1950-1951, they will make available to students in the Faculty of Medicine, scholarships of $200 to be awarded in each year of the course, making a total of $1200. In addition there will be available four bursaries of $100 each obtainable by a student in any year.

Since this Alumni Association scholarship project was commenced in 1943, it has grown steadily in value and interest. The officers and members of the Association like to think that it constitutes a tangible link between the students of the present generation and those who have enjoyed the privilege of securing their Medical education at the University of Toronto.

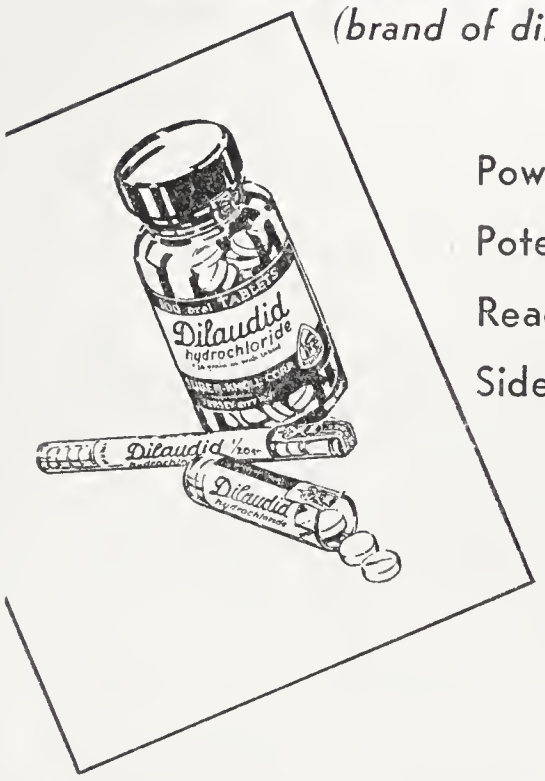
Graduates are reminded that they may assist this effort by sending a cheque to the Scholarship Fund.

R. L. SMITH

Dilaudid hydrochloride

(brand of dihydromorphinone hydrochloride)

COUNCIL ACCEPTED



Powerful opiate analgesic - dose, 1/32 grain to 1/20 grain.

Potent cough sedative - dose, 1/128 grain to 1/64 grain.

Readily soluble, quick acting.

Side effects, such as nausea and constipation, seem less likely to occur.

An opiate, has addictive properties.

Dependable for relief of pain and cough, not administered for hypnosis.

• Dilaudid, T. M. Reg. Canada

Product of Bilhuber Knoll Corp., Orange, N. J.

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WELCH ALLYN OPHTHALMOSCOPE

With Illuminating and Lens System as devised by Dr. C. H. May

In addition, has a Sliding Diaphragm Device giving

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- PIN HOLE APERTURE
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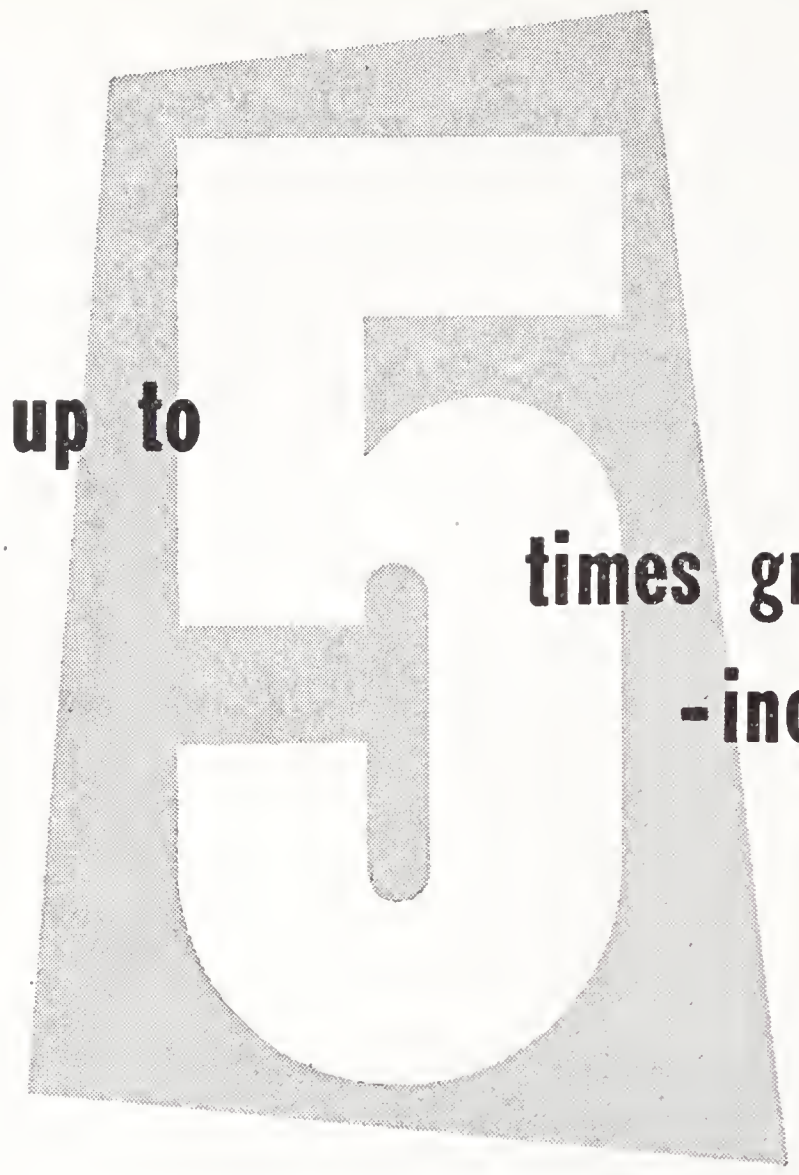
MONTREAL TORONTO HALIFAX



times greater absorption
-increased retention

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water-dispersible vitamin drops

Clinical tests indicate that when Vitamin A is given in a water-dispersible rather than an oily vehicle, up to five times greater absorption takes place. Similarly storage of both Vitamins A and D is also greatly increased and excretion is less.

"ALPHAMETTE" Aqueous No. 929

Each drop contains approximately:
Vitamin A.....1,000 I.U.
Vitamin D..... 500 I.U.
The suggested daily dase is 2 drops.
In bottles of 8, 15 ond 30 cc. with dropper.

"SUPPLAVITE" Drops No. 931

The average daily dase of 10 drops (0.6 cc.) provides approximately:
Vitamin A.....5,000 I.U.
Vitamin D.....1,000 I.U.
Ascorbic Acid..... 50.0 mg.
Thiamine..... 1.5 mg.
Ribaflavin..... 1.0 mg.
Niacinamide..... 20.0 mg.
Pyridoxine..... 1.0 mg.
Calcium d-Pantothenate... 5.0 mg.
Mixed Natural Tocopherols (as Antioxidant)..... 2.0 mg.
In bottles of 8, 15 and 30 cc. with dropper.

Ayerst

Ayerst, McKenna & Harrison Limited

Biological and Pharmaceutical Chemists • MONTREAL, CANADA

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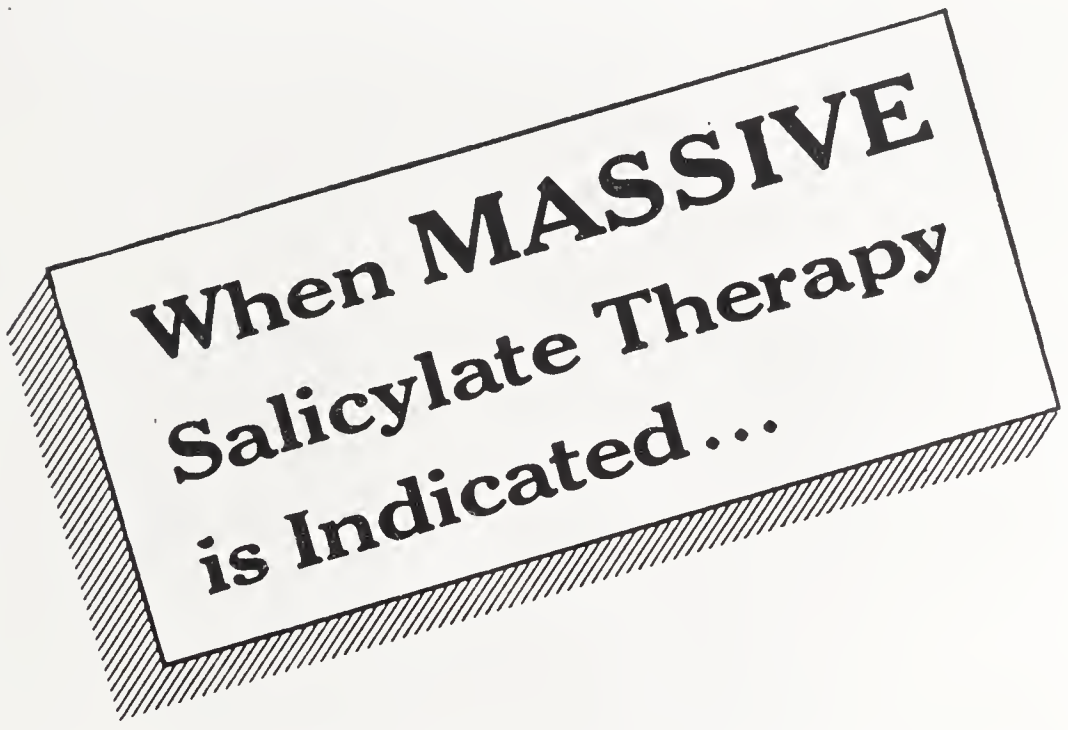

toxic effects, such as depression of blood prothrombin and hemorrhagic tendency, are avoided by the administration of

BEREX—*the NON-TOXIC product of choice*

because it provides, in tablet form, an easily administered and scientifically-balanced combination of calcium succinate and acetylsalicylic acid.

Full details concerning BEREX in the treatment of acute and chronic rheumatism, with extensive bibliography, available on request.

Available in bottles of 100 and 500 tablets.

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have developed these products, all of which are rapidly receiving the greatest commendation in Canada, France, Great Britain and the United States for their extreme originality and their donation to medical advancement

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Limited

Montreal

For the Modern Medicine-Man . . .

THE BELLA COOLA INDIANS

By T. F. McIlwraith

Photographs
Diagrams
Price $15.00

Ancient medical customs and tribal habits are depicted here by a man who gathered his information at first-hand. Prof. McIlwraith lived for a year with these primitive people and in these two volumes presents an authoritative and comprehensive account of their life and times.

"One can but wish that more such studies might appear; perhaps they will, from the pen of some student inspired by McIlwraith's teaching and example."—*Canadian Geographical Journal.*

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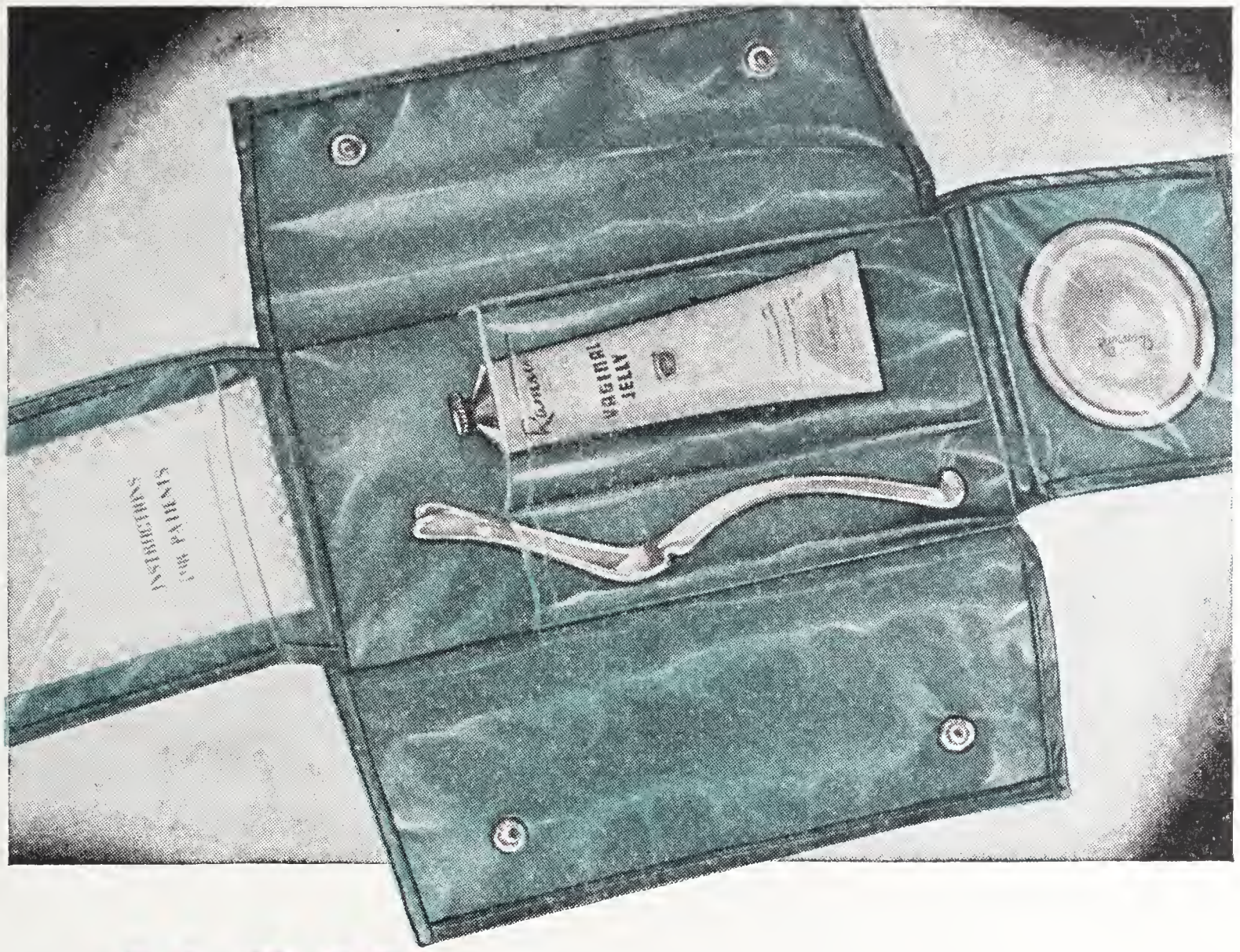
Trade Orders: S. J. R. Saunders



NOW.. ADDED CONVENIENCE FOR THE PATIENT

The "RAMSES"* "Tuk-A-Way Kit" provides added convenience for the patient, for tucked into this colorful, washable plastic kit she will find all the units essential for optimum protection.

The Tuk-A-Way Kit packs inconspicuously in the corner of a travelling bag or dresser drawer. It is available to patients through all licensed pharmacies.

Julius Schmid (Canada) Ltd.

31 Teraulay Street
TORONTO, ONTARIO

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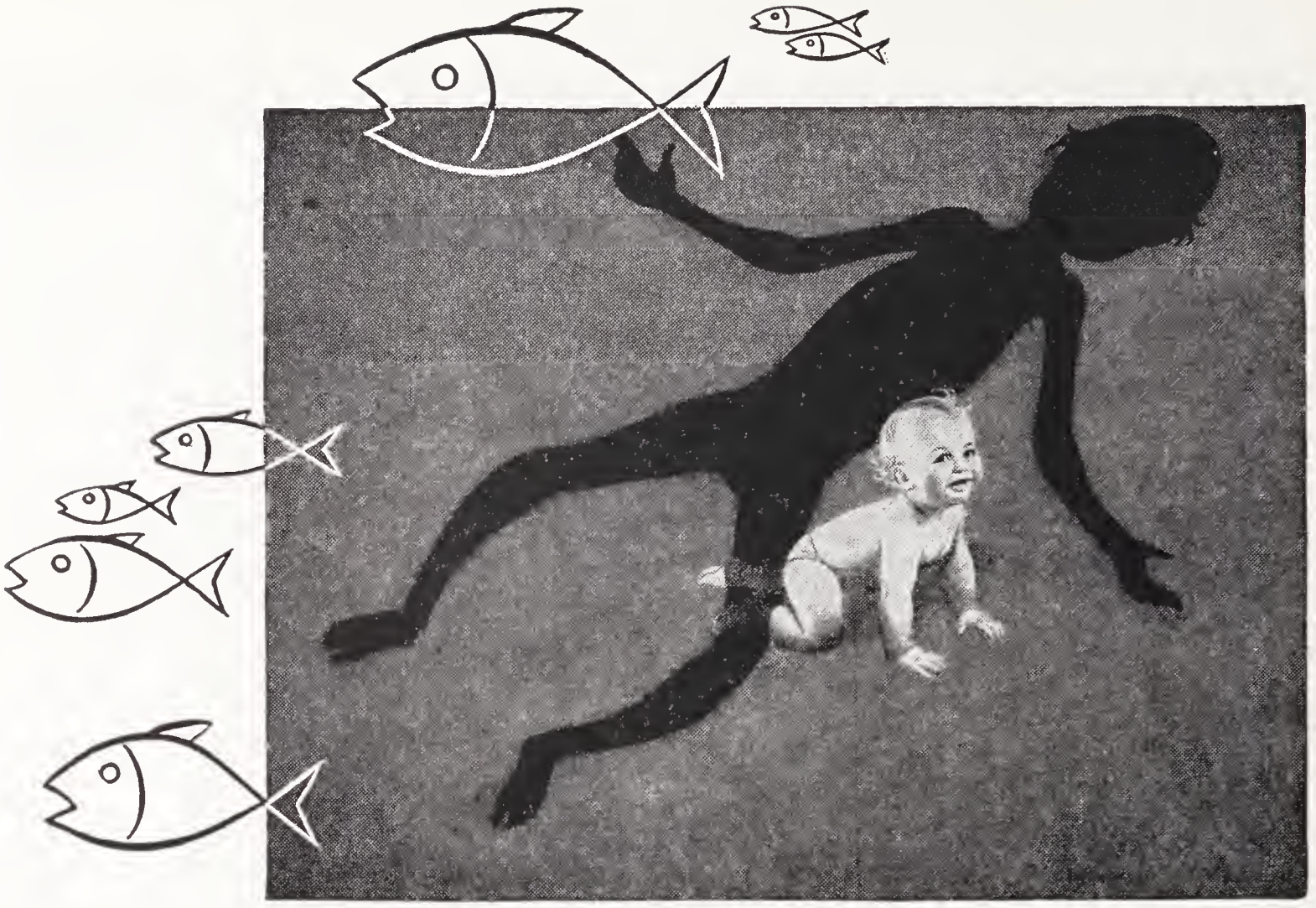


Supplements the sun...

removes the shadow of ***RICKETS***

Rickets may be found in apparently healthy and well nourished infants due to an insufficient intake of vitamin D plus inadequate exposure to ultraviolet rays.

It is now generally accepted that a vitamin D supplement should be given regularly not only to infants but to older children and adolescents. Mead's Oleum Percomorphum With Other Fish Liver Oils and Viosterol is useful for this purpose.

Mead's Oleum Percomorphum

1. Is a highly potent† source of natural vitamins A and D.

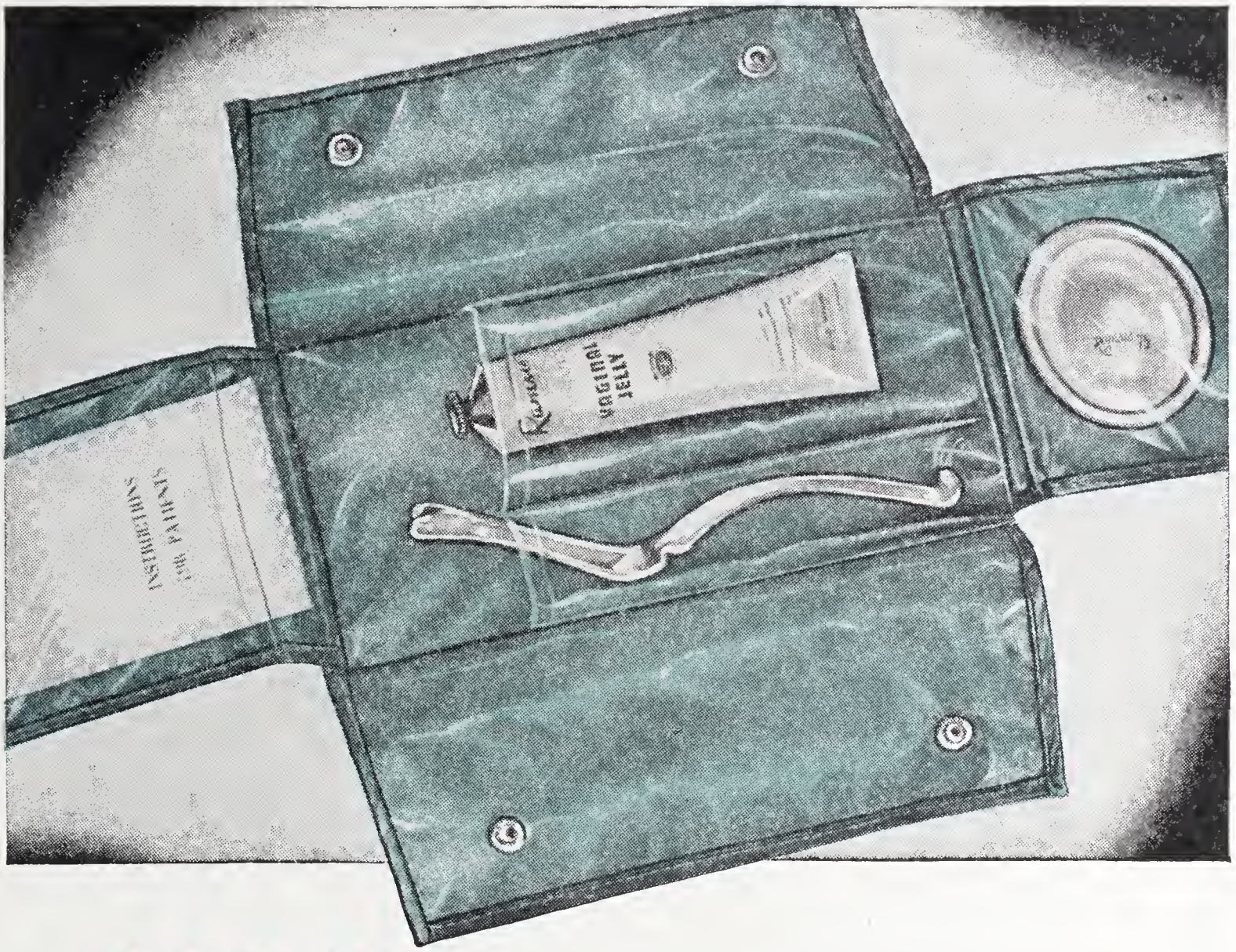
2. May be given in drop doses that are easily administered and well tolerated, and is supplied in capsule form also.

3. Has a background of sixteen years of successful clinical use.

†Potency: 60,000 U.S.P. units of vitamin A and 8500 U.S.P. units of vitamin D per gram. Each drop supplies 1250 units of vitamin A and 180 units of vitamin D; each capsule, 5000 units of vitamin A and 700 units of vitamin D.

Supplied in 10 cc. and 50 cc. bottles; and in bottles of 50 and 250 capsules.

Local Representative: J. D. Langlois, Jr.,
25 Kingsgarden Road, Toronto 10, Ontario, Canada, Lyndhurst 8055.



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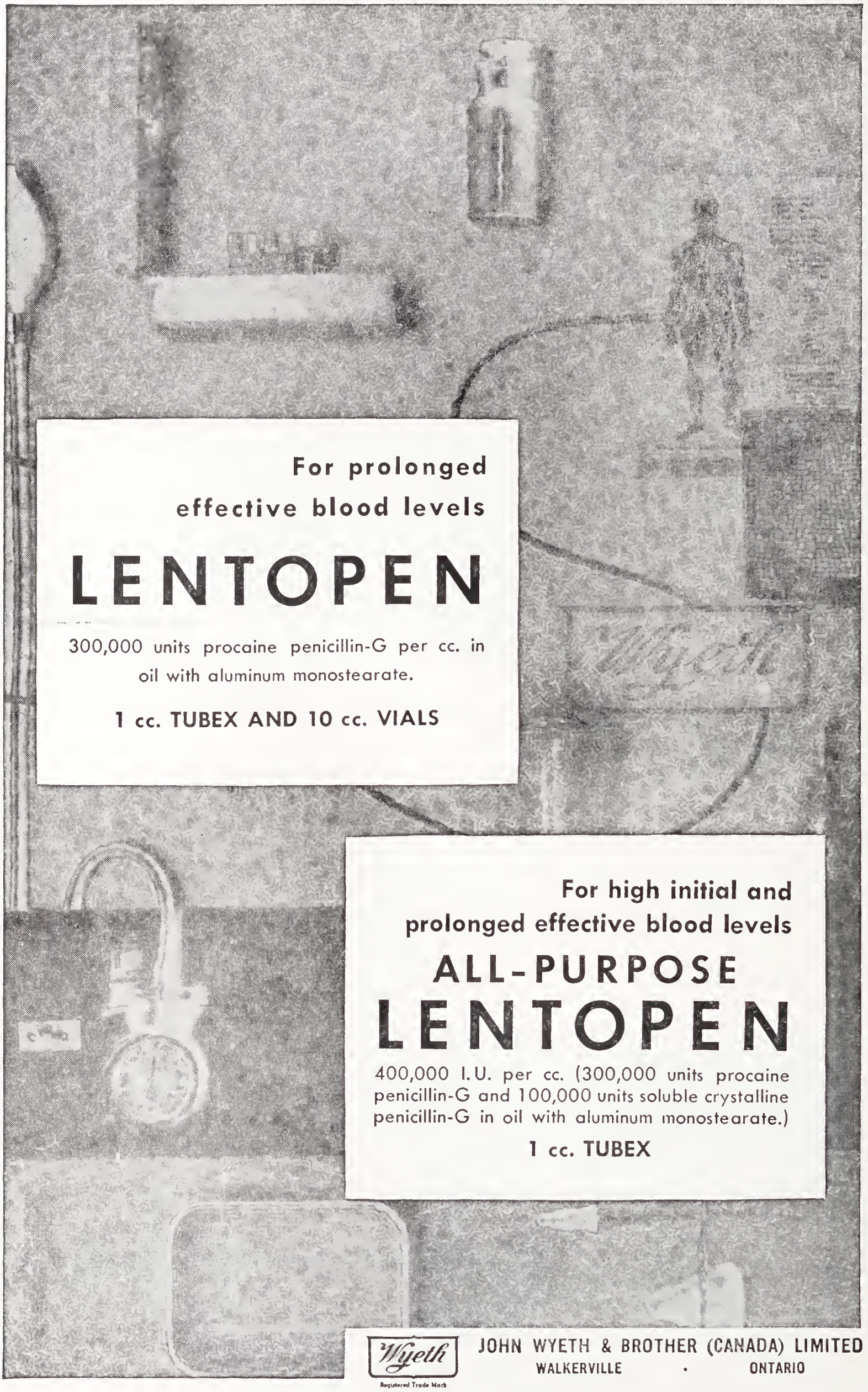

For prolonged
effective blood levels

LENTOPEN

300,000 units procaine penicillin-G per cc. in oil with aluminum monostearate.

1 cc. TUBEX AND 10 cc. VIALS

For high initial and
prolonged effective blood levels

ALL-PURPOSE
LENTOPEN

400,000 I.U. per cc. (300,000 units procaine penicillin-G and 100,000 units soluble crystalline penicillin-G in oil with aluminum monostearate.)

1 cc. TUBEX

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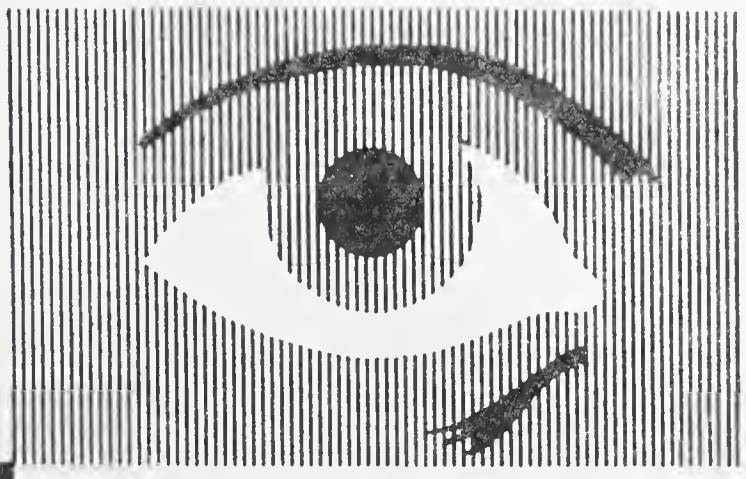
Registered Trade Mark

JOHN WYETH & BROTHER (CANADA) LIMITED
WALKERVILLE · ONTARIO



Clinically proved . . .

therefore preferred

truly therapeutic dosages of all the individual vitamins known to be essential in human nutrition.

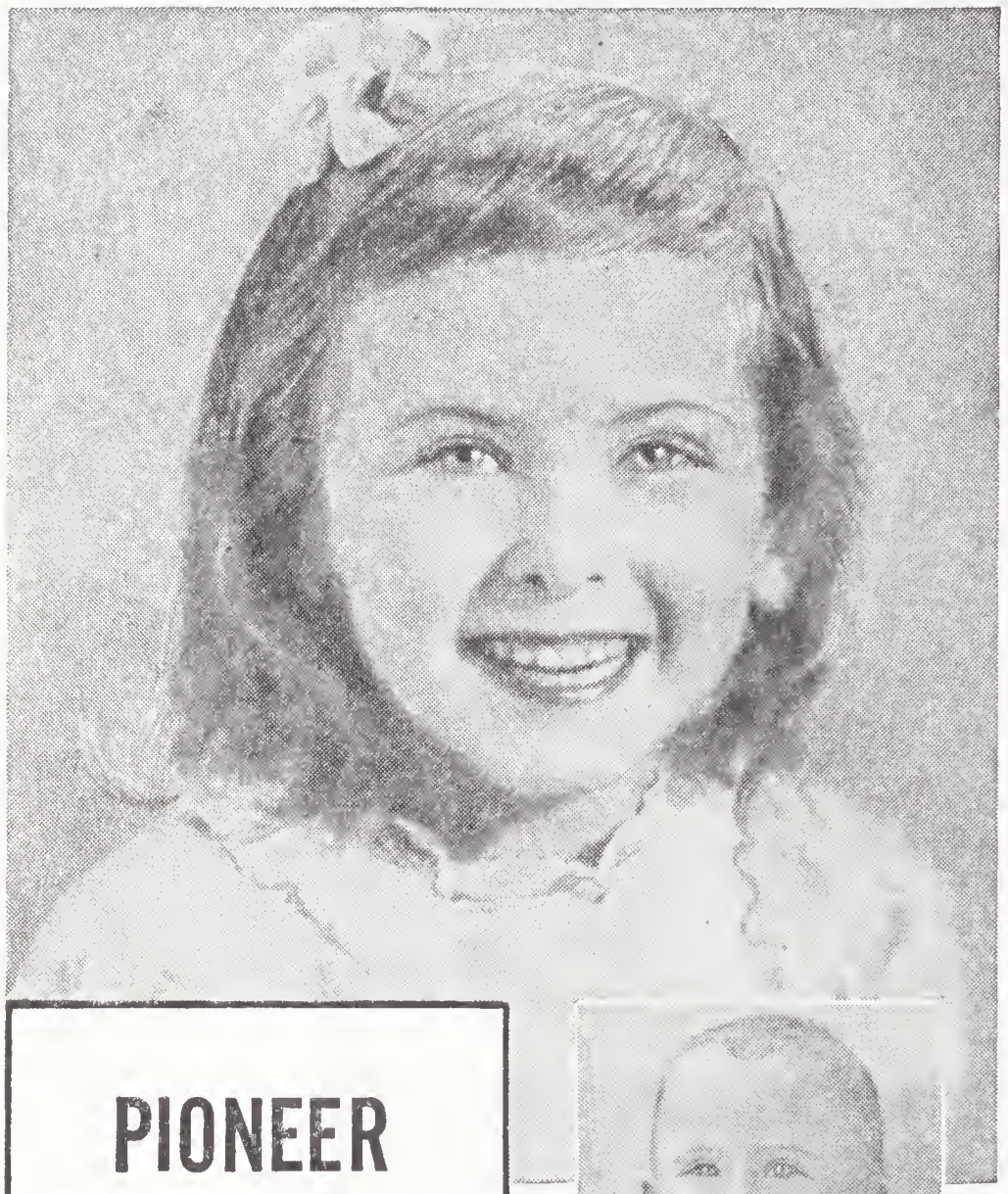
THERAPEUTIC FORMULA

VITAMIN CAPSULES **SQUIBB**

the standard of comparison *Bottles of 100 capsules*

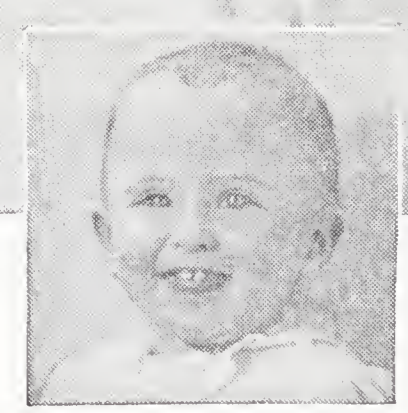
E. R. SQUIBB & SONS OF CANADA LIMITED
2245 VIAU STREET, MONTREAL

SQUIBB *Manufacturing Chemists to the Medical Profession since 1858*



PIONEER MEAT EATER

(5 years later)



Five years ago, little Betsy Traynor was a participant in Swift's Meats for Babies first feeding test.

Current Clinical Meat Feeding Studies

REPORT No. 1

MEAT FOR ALLERGY FEEDING

From this research has evolved a milk substitute for feeding to allergic infants and children who cannot tolerate milk. The formula, which may be easily made up by the mother, consists of Swift's Strained Beef supplemented with calcium, phosphorus salts, carbohydrate and fat. Studies show that the calcium, phosphorus and protein are utilized as well as these same nutrients when derived from milk.

This study on the nutritional value of a meat formula is part of an extensive clinical research program now being conducted through grants-in-aid made by Swift.

Way back when Betsy started Swift's Meats, meat was a "revolutionary" food for a baby. Betsy and her fellow participants were the first babies *ever* to eat Swift's specially prepared strained meats. Many of the infants in this original group were only six weeks old at the time!

Betsy's bubbling good spirits and sound, sturdy development testify to the benefits of regular meat-feeding early in life. And Betsy's mother will tell you, "She's the very picture of health!"

Today any baby can have the same right start in life that lucky little Betsy had. Doctors recommend Swift's Meats for Babies now in the early weeks of life—to provide the complete high-quality proteins and iron every infant needs every day for sound growth and development.

Swift prepares an appetizing variety of: beef, lamb, pork, veal, liver and heart—to help infants form sound eating habits.

Swift's Meats for Babies are expertly trimmed to minimize fat content—carefully cooked to preserve a maximum of essential meat nutrients. Swift's Strained Meats for Babies—Diced Meats for Juniors—are convenient and economical, cost less than home-prepared meats.

ACCEPTED COUNCIL ON FOODS AND NUTRITION AMERICAN MEDICAL ASSOCIATION

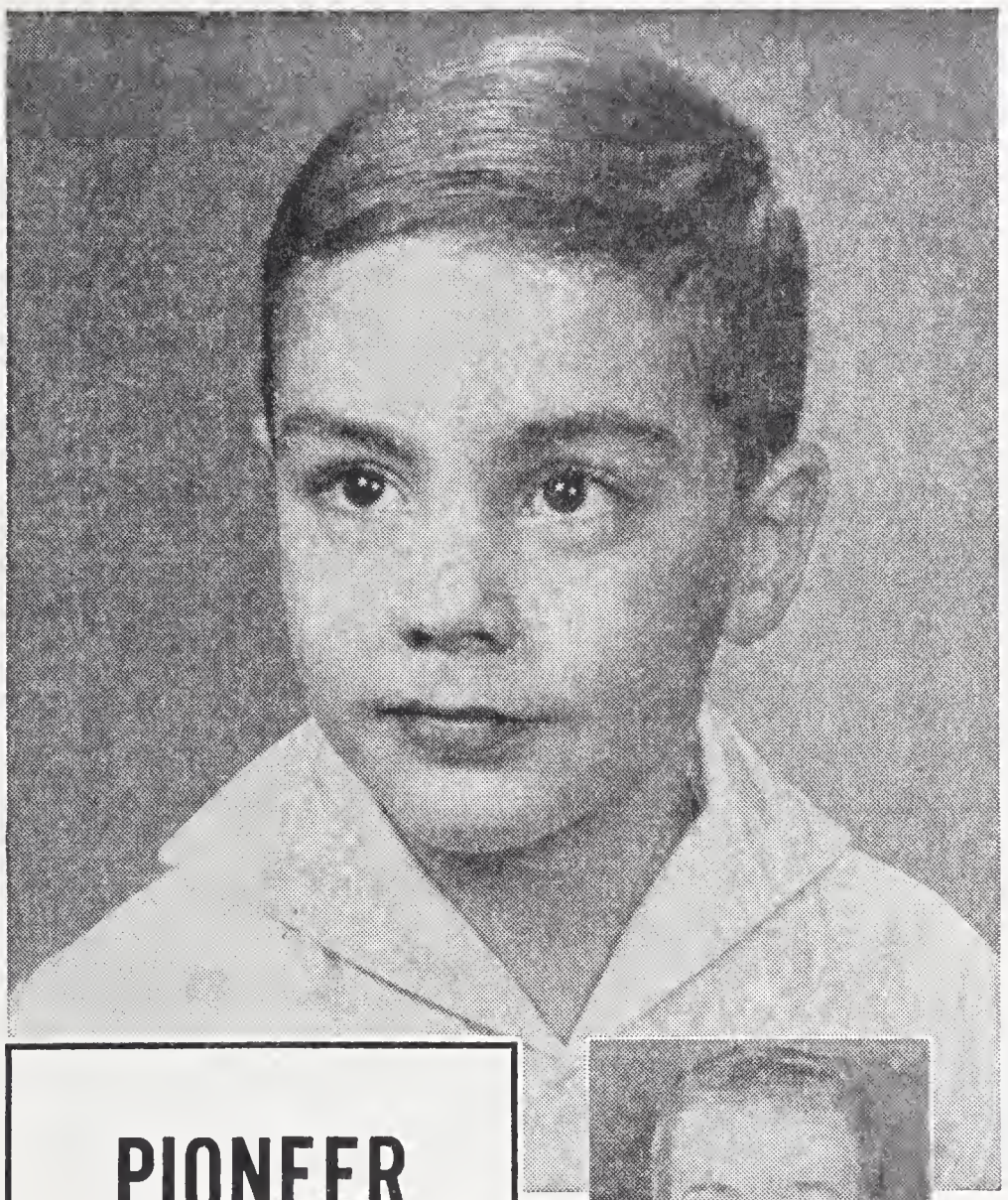
All nutritional statements made in this advertisement are accepted by the Council on Foods and Nutrition of the American Medical Association.

SWIFT QUALITY FOODS

SWIFT

...foremost name in meats

...first to develop and clinically test 100% Meats for Babies



PIONEER MEAT EATER

(5 years later)

Kenneth Clark Gorman participated in Swift's first meat-feeding test. Here he's shown at six months.

Current Clinical Meat Feeding Studies

REPORT No. 2

SLEEP CHARACTERISTICS OF THE HUMAN INFANT

An investigation of the sleeping habits of infants six to twenty-six weeks of age is being made in this study. The effect of diet on the sleeping habits of the infants under study is one phase of the investigation. The test diet contains Swift's Strained Meats. Special apparatus attached to the cribs records the movement of the children and indicates their periods of sleeping and wakefulness.

This study is part of an extensive clinical research program now being conducted through grants-in-aid made by Swift's.

In Swift's original test feedings, Kenny Gorman started Swift's Meats for Babies at *three months*—right along with his first solid foods. Contrast this with the general practice five years ago. Before the development of specially prepared Swift's Meats for Babies, the customary age to start meat was *six* or *nine* months. And because home-preparation was so difficult, most babies simply went without!

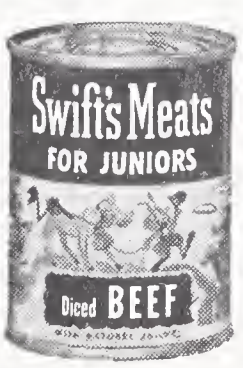
He's big and husky now

Kenny's mother will verify the fact that he's as "big and husky" as he looks in his photograph. Says Mrs. Gorman, "He can hold his own against my other three children."

Today any baby can have the same right start in life that little Kenny had. Doctors now recommend Swift's Meats for Babies in the early weeks of life—to provide the complete, high-quality proteins and iron every infant needs every day.

Swift's appetizing variety includes: beef, lamb, pork, veal, liver and heart—to help infants form sound eating habits.

Swift's Meats for Babies are expertly trimmed to minimize fat content . . . carefully cooked to preserve a maximum of essential meat nutrients.



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SWIFT QUALITY FOODS

SWIFT

. . . foremost name in meats

. . . first to develop and clinically test 100% Meats for Babies

Dilaudid hydrochloride

(brand of dihydromorphinone hydrochloride)

COUNCIL ACCEPTED

Powerful opiate analgesic - dose, 1/32 grain to 1/20 grain.

Potent cough sedative - dose, 1/128 grain to 1/64 grain.

Readily soluble, quick acting.

Side effects, such as nausea and constipation, seem less likely to occur.

An opiate, has addictive properties.

Dependable for relief of pain and cough, not administered for hypnosis.

● Dilaudid, T. M. Reg. Canada

Product of Bilhuber Knoll Corp., Orange, N. J.

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have developed these products, all of which are rapidly receiving the greatest commendation in Canada, France, Great Britain and the United States for their extreme originality and their donation to medical advancement

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Samples and literature available upon request

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POULENC

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Facts for Quick Reference

THE INTERMEDIATE SEDATIVE

"NOCTINAL"

"Frosst" brand of Butabarbital N.N.R.

FOR SEDATION, HYPNOSIS AND TO AUGMENT THE ACTION OF ANALGESICS.

The duration and intensity of effect of Noctina is intermediate between that of quick-acting pentobarbital and long-acting phenobarbital.

"NOCTINAL"

- acts promptly — within half an hour.
- in therapeutic doses, has no toxic effect on heart, respiration, blood pressure or kidney.
- is quickly eliminated — effects wear off in 4 to 6 hours.
- is non-cumulative — patients awake refreshed, without depression after a sound, restful sleep.

"NOCTINAL"

S.C.T. No. 352 "Frosst"
Noctinal sodium..... ½ gr. (32 mg.)
S.C.T. No. 419 "Frosst"
Noctinal sodium..... ¾ gr. (50 mg.)
S.C.T. No. 353 "Frosst"
Noctinal sodium.....1½ gr. (97 mg.)

DOSAGE

For mild, continuous sedation: ½ to 1 grain, 2 or 3 times daily. In insomnia: 1½ to 3 grains about one-half hour before retiring. In excited states: 1½ to 3 grains, 2 to 3 times a day. Children: according to age and physical condition.

MODES OF ISSUE

Bottles of 100 and 500 tablets.

Complete therapeutic information and clinical samples available on request.

"NOCTINAL" ELIXIR

Elixir No. 601 "Frosst"

Each fluid ounce contains:
Noctinal sodium .....4 grs. (0.26 G.)

DOSAGE

Adults: 2 to 3 fluid drachms in a wineglass of water. Maximum daily dose, two fluid ounces. Children: according to age and physical condition.

MODES OF ISSUE

16 fluid ounce and ½ Imp. gal. bottles.

Frosst
SINCE 1899
THE SYMBOL OF PROGRESS IN PHARMACEUTICAL RESEARCH

Charles E. Frosst & Co.
MONTREAL CANADA

Facts for Quick Reference

"ALAMINO"

"Frosst" brand of Aluminum glycinate (basic)

for the treatment of PEPTIC ULCER and HYPERACIDITY

ALAMINO OFFERS 5 ADVANTAGES

- Prompt relief of pain in uncomplicated "peptic ulcer" cases.
- Rapid and prolonged antacid action without danger of alkalosis.
- High acid-buffer capacity with minimum aluminum content — 40% less than dried aluminum hydroxide.
- Immediate dispersion in stomach contents.
- Small, pleasant-tasting tablets, no need to chew. Readily carried in pocket or purse.

"ALAMINO" COMPOUND TABLETS

C.T. No. 382 "Frosst"

Each tablet contains:
Alamino.....7.7 gr. (0.5 G.)
Atropine sulphate 1/500 gr. (0.13 mg.)
"Noctinal" sodium 1/4 gr. (16 mg.)
"Frosst" brand of Butabarbital N.N.R.

DOSE

1 to 2 tablets, after meals and at bedtime.

MODES OF ISSUE

Bottles of 100 and 500 tablets.

"ALAMINO" TABLETS

C.T. No. 381 "Frosst"

Each tablet contains:
Alamino.....7.7 gr. (0.5 G.)

DOSE

1 to 2 tablets, after meals and at bedtime.

MODES OF ISSUE

Bottles of 50, 100 and 500 tablets.

"ALAMINO" SUSPENSION

Each teaspoonful (4 cc.) contains:
Alamino.....7.7 gr. (0.5 G.)

DOSE

1 to 2 teaspoonfuls after each meal and at bedtime

MODES OF ISSUE

16-ounce bottles.

Complete therapeutic information and clinical samples available on request.

Frosst SINCE 1899 THE SYMBOL OF PROGRESS IN PHARMACEUTICAL RESEARCH

Charles E. Frosst & Co.
MONTREAL CANADA

How Heinz safeguards the babies in your care

Heinz Baby Foods are dated to ensure fresh stocks

Every tin of Heinz Strained and Junior Foods carries a *code number*, showing the date it was packed—the day and the year. Heinz salesmen check these numbers when they make their frequent visits to grocers' and druggists' stores, to make certain that the supplies in stock are always fresh.

Heinz takes this *special precaution* in order to be doubly sure that infants will get foods of the fine fresh quality that is so important in baby diets.

This checking at the point of sale is the last of several steps Heinz takes—from the selection and cleansing of the raw materials, through to the Quality Control Laboratories —all aimed at inspiring confidence in its products among doctors, nurses and mothers.

Heinz Baby Foods

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27 STRAINED FOODS, 17 JUNIOR FOODS, 2 BABY CEREALS

BARDONA CAPSULE

a new gastric sedative and antispasmodic

Will.

Pentobarbital is effective as a sedative in heightened nervous conditions which so frequently accompany gastric disturbances. The beneficial effects of the barbiturates in nausea and vomiting, as in seasickness, pregnancy, vertigo and migraine, are well known.

Belladonna with its chief alkaloids atropine and hyoscine, relieves spasm of pyloris and other sphincters and at the same time prevents excessive contractions of the stomach and intestines.

Each capsule contains:

Sodium Pentobarbital . . . . . ¼ grain

Powdered Extract Belladonna B.P. . ¼ grain

Available in bottles of 100, 500, 1,000.

ETHICAL PHARMACEUTICAL PRODUCTS

CHARLES R. WILL & COMPANY LIMITED

LONDON, CANADA